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THE UNIVERSITY OF ALBERTA

CHEMISTRY AND PHARMACOLOGY OF 1-AZAXANTHONES

BY

SATYA S. MURTHY

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SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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The undersigned certify that they have read, and recommend to the faculty of graduate studies and research for acceptance, a thesis entitled CHEMISTRY AND PHARMACOLOGY OF 1-AZAXANTHONES submitted by SATYA S. MURTHY in partial fulfilment of the requirements for the degree of Doctor of philosophy in Pharmaceutical sciences (Medicinal chemistry).

Supervisor

External examiner

Date: 25 Nov., 1987

To my family

ABSTRACT

Arachidonic acid is metabolised by cyclooxygenase and lipoxygenase. Non-steroidal anti-inflammatory drugs inhibit cyclooxygenase and consequently prostaglandin synthesis. The leukotrienes are lipoxygenase-mediated products which appear to play a role in such conditions as asthma, allergy, arthritis and psoriasis. The development of agents which modulate the synthesis or actions of leukotrienes, may lead to significant improvements in the therapy of inflammatory and immediate hypersensitivity disease states.

5H-[1]Benzopyrano[2,3-b]pyridin-5-one (1-azaxanthone) derivatives are known to possess anti-inflammatory and anti-allergic properties. It was therefore desirable to develop enzyme inhibitors which incorporate the 1-azaxanthone nucleus. Structural modifications were conducted at four sites: the pyridine ring, the heteroatom bridge, the benzene ring and the C-5 position. Catalytic hydrogenation of 1-azaxanthone derivatives gave a series of 5H-[1]benzopyrano[2,3-b]-1,2,3,4-tetrahydropyridin-5-ones (74 a-h). Methyl iodide salts of 1-azaxanthones were ring-opened to give 3-benzoyl-1-methyl-2(1H)-pyridinones (80 a-k). Sodium borohydride reduction of 1-azaxanthone derivatives in methanol and then in acetic acid gave 1-azaxanthene analogs. Modifications at the benzene ring afforded compounds with five or six membered heterocyclic rings fused across the C-6,7 or C-7,8 positions; five membered rings included imidazole (90, 94, 99), triazole (100, 101, 102), thiazole (103, 105), pyrrole (108 a-f), furan (113, 116), dihydrofuran (112, 114), oxadiazole (120) and oxazole (121); six membered rings included pyridine (123), dioxane (124), dihydrooxazine (126) and pyrone (132).

The pharmacological models used to screen potential lipoxygenase inhibitors and cyclooxygenase inhibitors were the guinea pig spirally cut trachea and lung parenchyma strips. The former tissue (indomethacin-treated) revealed lipoxygenase-inhibiting properties and the latter cyclooxygenase antagonism. The pD_2 values (i.e negative log of concentration that inhibited the arachidonic acid-induced contraction by 50%) were determined and compared to known lipoxygenase and cyclooxygenase inhibitors. The

lipoxygenase inhibitors nafazatrom and piriprost showed pD_2 values of 4.15 and 4.68, respectively. The most active compound was a thiazole derivative (105) which gave a pD_2 value of 7.68 (trachea) and had moderate bronchodilating properties.

Preliminary structure activity relationships were drawn based on pharmacological results.

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LIST OF ABBREVIATIONS

bp	--- boiling point
cm	--- centimeter
^0C	--- degrees celsius
$CDCl_3$	--- deuterochloroform
DMSO-d_6	--- hexadeuterodimethyl sulfoxide
g	--- gram
hr	--- hour
ir	--- infrared
min	---minute
mp	--- melting point
mmol	--- millimole
ml	--- milliliter
mol	--- mole
nmr	--- nuclear magnetic resonance
psi	--- pounds per square inch
TLC	--- thin layer chromatography

I. INTRODUCTION

1.0. INFLAMMATION AND ITS MEDIATORS:

Inflammation is defined as the body's response to tissue injury. It is characterised by heat, redness, swelling and loss of function. It usually acts as a protective mechanism for the host. When the inflammatory process persists for an extended period of time, as in chronic arthritis, it can lead to progressive local tissue destruction and chronic pain, and hence become detrimental to the body.

1.1. **Molecular mediators of inflammation:**[1]

The various mediators involved in the process of inflammation are:

1.1.1. Histamine:

Histamine is a low molecular weight compound stored as a complex with heparin in mast cells and basophils. It causes dilatation of the terminal arterioles and increases vascular permeability of post-capillary venules. This effect is only transient and contributes to the early stages of an acute inflammation. Hence some of the inflammatory edemic response can be inhibited by administration of an antihistamine drug like mepyramine.

1.1.2. 5-Hydroxytryptamine: (Serotonin, 5-HT)

In mammals 5-HT is stored mainly in enterochromaffin cells of the gastro-intestinal tract. It is considerably more potent than histamine in increasing vascular permeability. In experimental animals the early stages of carrageenin-induced paw edema have been shown to be dependent on simultaneous release of both histamine and 5-HT. Treatment with histamine and 5-HT antagonists effectively suppresses early development of edema.[2,3]

1.1.3. Plasma kinins:

The plasma kinins include the peptides bradykinin and kallidin, both of which can mediate an increase in vascular permeability and a dilatation of arterioles. Their effects appear to contribute to a transitory phase (1-2 hr) of acute inflammatory response

following histamine and 5-HT.[2,3] They are generated in plasma from their precursors, kininogens.

1.1.4. EICOSANOIDS: (Prostaglandins, Leukotrienes and Thromboxanes)

1.1.4.1. PROSTAGLANDINS:

Prostaglandins (PGs) are pro-inflammatory compounds synthesized locally. They potentiate inflammation, provoke fever and intensify pain. The precursor for prostaglandin production, arachidonic acid, occurs in every major cell type. Injured cells synthesize and release prostaglandins into the site of inflammation. The relationship of prostaglandins to inflammation was inferred from the discovery by Vane[12] in 1971, that aspirin and related compounds inhibited the synthesis of prostaglandins. These investigators also postulated that the major pharmacological effects of non-steroidal anti-inflammatory drugs (NSAIDs) may be accounted for by the ability of these compounds to inhibit prostaglandin synthesis.

Arachidonic acid is stored in phospholipids in cell membrane (Fig. 1). Prostaglandin synthesis is initiated by the cleavage of arachidonic acid from membrane phospholipids through the action of phospholipases. Complex rearrangement, including the addition of two molecules of oxygen, results in the formation of the characteristic five-membered prostaglandin ring.

1.1.4.1.1. Functions of prostaglandins related to inflammation:[4]

Several prostaglandins, especially PGE_2, PGI_2 and possibly PGD_2, contribute to inflammation by increasing blood flow (erythema), by dilating blood vessels and increasing capillary permeability (edema) and by increasing pain sensitivity to other mediators such as bradykinin and histamine. Prostaglandins also have pyretic effects under some conditions such as following the release of leukocytic pyrogen and endotoxin.[5,6]

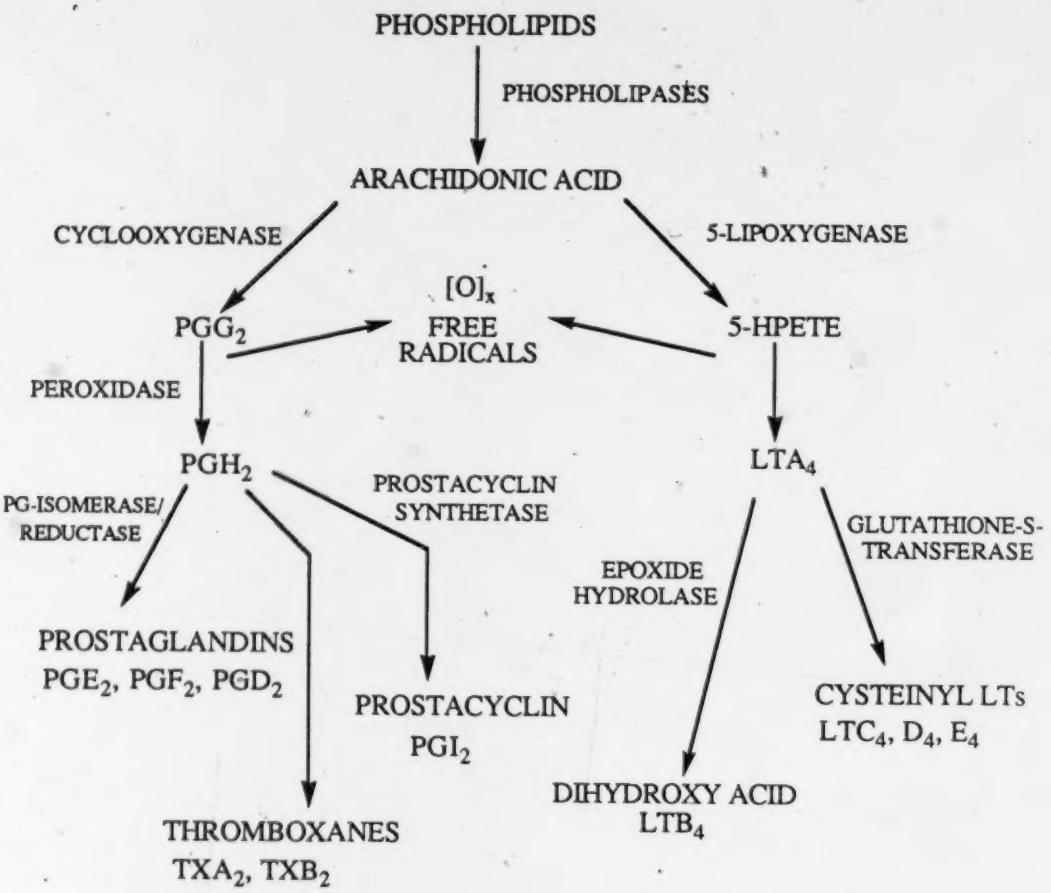


Fig. 1: Arachidonic acid cascade.

1.1.4.2. LEUKOTRIENES: (LTs)

This important class of eicosanoids was discovered in 1979 by Samuelsson.[7] The leukotrienes bear some resemblance to prostaglandins in that they are also products of the reactions of molecular oxygen and arachidonic acid. However they lack the five or six membered ring structures seen in prostaglandins (Fig. 2).

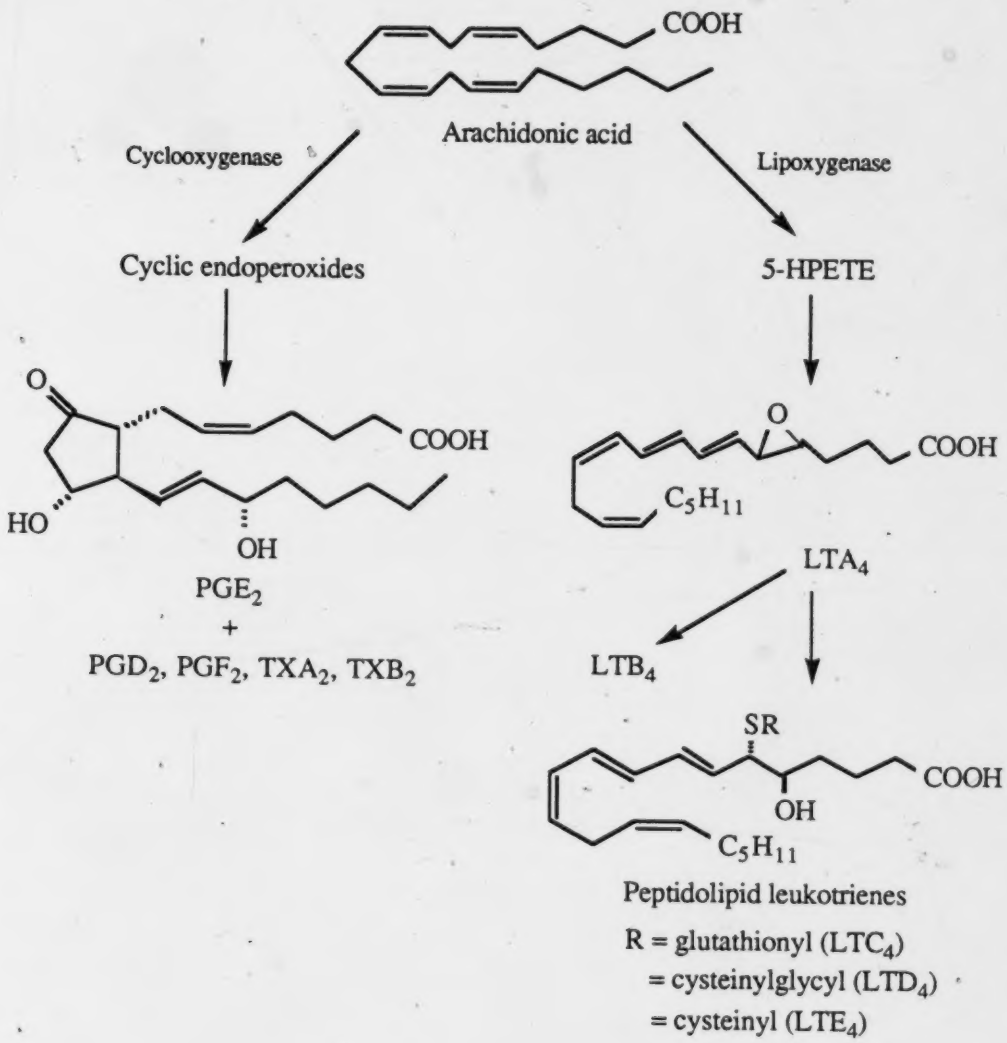


Fig. 2: Structures of some prostaglandins and leukotrienes.

1.1.4.2.1. Biological functions of leukotrienes related to inflammation:[8]

LTB_4(Dihydroxy acid)	LTC_4, D_4, E_4 (Cysteinyl LTs)
chemotaxis	contraction of smooth muscle
chemokinesis	bronchoconstriction
aggregation of PMNs	vasoconstriction
increased vascular permeability	secretion of mucus
exudation of plasma	stimulation of phospholipase

LTB_4 is a very potent chemotactic factor for neutrophils, eosinophils and mononuclear cells.[9] LTB_4 also activates neutrophils by causing degranulation and superoxide generation. LTB_4 has been isolated from synovial fluids from patients with rheumatoid arthritis and gout[10] and fluids from involved skin of psoriactics.[11] Thus LTB_4 could be an important mediator of leukocyte influx at sites of inflammation. Therefore inhibition of LTB_4 synthesis represents an attractive therapeutic goal.

The peptido-lipid or cysteinyl leukotrienes (LTC_4, D_4, E_4) also have inflammatory activities in the skin causing wheal and flare responses.[13] Although cysteinyl leukotrienes are involved in inflammation, most interest is directed to their role as potential mediators of bronchoconstriction occurring in asthma and similar hypersensitivity reactions. They are the major components of slow-reacting substance of anaphylaxis (SRS-A), which causes prolonged contraction of bronchial smooth muscle.[14] Thus, inhibition of arachidonic acid metabolism via the 5-lipoxygenase pathway is a valuable strategy for development of new anti-inflammatory and anti-asthmatic agents.

It should be noted that eicosanoids act primarily as potentiators (or in some cases as moderators), rather than initiators of inflammation. Both prostaglandins and leukotrienes are synthesized when they appear to be needed in tissues. They are not stored in appreciable quantities in either cells or tissues. They are secreted shortly after their

biosynthesis and act on cells in the vicinity of their cell of origin. In this way they differ from circulating hormones.

1.1.4.3. THROMBOXANES: (TXs)

Thromboxane A_2 and B_2 are produced by the action of thromboxane synthetase on PGH_2. Thromboxane A_2 a major arachidonic acid product of platelets, is a potent vasoconstrictor, platelet aggregatory stimulator and bronchoconstrictor.[15] Following vascular trauma, collagen and other factors stimulate platelet aggregation and thromboxane release. Thromboxane A_2 is extremely unstable in aqueous solution. It is rapidly hydrolysed non-enzymatically to its more stable, but less active metabolite thromboxane B_2.[16]

2.0. INHIBITORS OF ARACHIDONIC ACID METABOLISM:

Corticosteroids have been known for their potent anti-inflammatory effects. Their mechanism of action is shown in Fig. 3. Since there are many unacceptable toxic side effects associated with corticosteroids, their use is limited. This led to the search for non-steroidal agents with similar activities but, with less severe side effects. NSAIDs have emerged in the past two decades, due to extensive chemical and pharmacological efforts. The mechanism of action of NSAIDs was first reported by Vane.[12]

2.1. **Inhibition of cyclooxygenase pathway:**[17]

Virtually all the NSAIDs have been shown to inhibit the synthesis of prostaglandins by inhibiting the cyclooxygenase enzyme. The NSAIDs in general do not have major effects on the lipoxygenase pathways, but there are some exceptions (e.g.benoxaprofen). The inhibition of the cyclooxygenase enzyme system by NSAIDs varies considerably according to the structural characteristics of each drug. The range of compounds which inhibit the cyclooxygenase enzyme is so extensive that it is not possible to say a specific

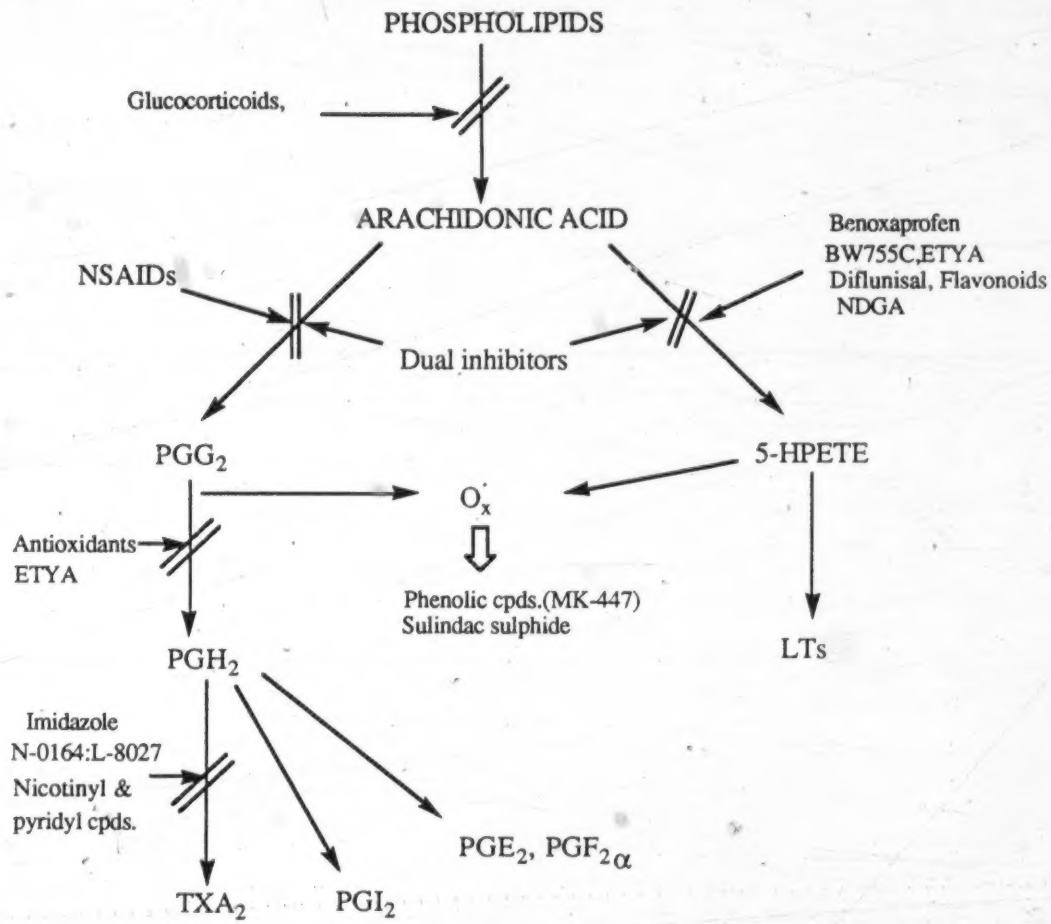


Fig. 3: Drug effects on eicosanoid metabolism.

property of those drugs is contributing to the anti-inflammatory activity. However some general physical and chemical properties of cyclooxygenase inhibitors can be summarised as follows.

2.1.1. GENERAL STRUCTURE ACTIVITY RELATIONSHIPS:

2.1.1.1. Hydrophobicity:

Hydrophobicity is one of the requirements for a NSAID. Like many other hydrophobic drugs, NSAIDs have a strong affinity for serum proteins, up to 95-99% of

NSAIDs are serum protein bound. This property may contribute significantly to their tissue distribution and duration of action *in vivo*. Since arachidonic acid is hydrophobic in nature, it is not surprising that hydrophobicity is a desirable characteristic for a substrate competitive inhibitor of cyclooxygenase.

2.1.1.2. Stereochemical requirements:

Most NSAIDs are substrate competitive inhibitors. A non-planar arrangement of an aromatic nucleus with another aromatic or aliphatic group can be seen in the structure of many NSAIDs (Fig. 4). Several hypothetical models comparing the stereochemistry of NSAIDs with a possible configuration of arachidonic acid at the active site of cyclooxygenase have been proposed.[18-20]

Scherrer[19] and Shen and Gund[18] have devised hypothetical requirements for the receptor site of the cyclooxygenase enzyme, based essentially on the fitting of drugs known to inhibit this enzyme. Scherrer's model incorporated a cationic site and two hydrophobic sites. Shen and Gund's model[18] was based on quantum chemical calculations of the interaction of indomethacin and related compounds with the receptor site. They postulated that the existence of a carboxy binding point, a hydrophobic region, and a second fatty acid binding hydrophobic region (groove) for interaction with a π electron system (of the drug). The weakness of these models is that many non-acidic compounds can inhibit cyclooxygenase, so that the requirement for a cationic site is not necessarily specific. Nevertheless these models do give a partial view of the structural requirements for inhibition by acidic biaryl acids.

According to Ushio Sankawa et al.,[20] the receptor site for the cyclooxygenase enzyme consists of four regions designated as α, ω, A and B. The α–region is provided with a cationic center trapping the carboxyl of arachidonic acid and the ω-region accommodates the terminal alkyl group. A and B are π electron acceptor regions

functioning as the catalytic sites for oxygenation at C_{11} and C_{15} of arachidonic acid. NSAIDs (e.g. ketoprofen) inhibit the reaction by occupying the active sites.

Appleton and Brown[21] have also suggested a template for designing NSAIDs. The template can be equated with a complementary cyclooxygenase receptor site. This process is based on the conformation of the peroxy radical immediately prior to its cyclization to PGG_2, and its structural similarity to the NSAIDs. This interpretation of the cyclooxygenase receptor site differs markedly from the proposals of Shen and Gund[18] and Scherrer.[19]

Perhaps the simplest situation for drug-induced inhibition of cyclooxygenase is seen with aspirin. It is clear that acetylation at or near the active site of the enzyme is a major feature of the mechanism of this drug.[22] It implies that there is a group at or near the active site capable of being esterified by this drug (e.g. the hydroxy of serine or threonine or the NH_2 groups of lysine). The acetylation is inhibited by arachidonic acid and indomethacin, suggesting common binding sites for all three compounds.

For cyclooxygenase inhibitors of the arylpropionic acid type (e.g. ibuprofen and naproxen), the stereochemistry of the chiral centre of the α–methylacetic acid side chain was recognised as being highly specific. The S(+) enantiomers are generally more active than the R(-) enantiomers *in vitro* as well as *in vivo*. In some cases for example, ibuprofen, naproxen and ketoprofen such differences become less prominent *in vivo*, possibly due to differential metabolism of two enantiomers and/or bioinversion of the chiral centre.[23]

2.1.1.3. Acidic function:

In the early study of NSAIDs, the presence of an acidic function e.g. carboxylic acid, tetrazole and acidic enol in substituted aryl or heteroaryl compounds was found to be highly desirable. The acidic group may compete with the carboxyl of arachidonic acid for enzyme binding. Later, it became apparent that the acidic function is not really essential for

cyclooxygenase inhibition.[24] Non-acidic agents, e.g. proquazone, tiflamizole[25] and timegadine were found to be potent cyclooxygenase inhibitors *in vitro* and effective anti-inflammatory agents *in vivo*. Furthermore the non-acidic agents generally cause less gastro-intestinal irritation in animal models.[26]

2.1.2. EFFECTS OF NSAIDs ON CELL MIGRATION AND ENZYME RELEASE:[27]

The cell population in an inflammatory exudate varies with time and with inflammatory stimulus. Certain cellular events such as arrival of polymorphonuclear leukocytes (PMNs) are common to all inflammatory response. These cells ingest foreign material and digest it by breaking it down with degradative enzymes stored within lysosomes. In a chronic inflammatory response the usually useful degradative enzymes contained within the lysosomes of phagocytic cells are inadvertently released into the inflamed area and eventually these enzymes produce local tissue damage.

Several NSAIDs have been reported to decrease the migration of total leukocytes into inflammatory exudates.[28] The mechanisms whereby the NSAIDs exert their effects against leukocyte migration are yet to be defined.

Several NSAIDs inhibit the release of lysosomal enzyme from PMNs *in vitro* and *in vivo*.[29] Changes in prostaglandin levels as well as effects of drugs, cause changes in cyclic nucleotide concentrations. This can influence the secretion of lysosomal enzymes by polymorphs and other cells.[30]

2.1.3. EFFECT ON OXYGEN FREE RADICALS:[27]

At the same time that damaging free radicals are released from phagocytic cells, oxygen-derived free radicals (such as superoxide anion and hydroperoxy radical) are also formed by these cells. The radicals cause local tissue damage and promote inflammation. Although short lived, oxygen radicals are very toxic to living tissue. Aspirin along with other NSAIDs have been found to inhibit superoxide production at pharmacological concentrations.[31] Inhibition, by NSAIDs, of the production of superoxide anions (O_2^-)

might also reduce the propensity of these radicals to induce lysosomal membrane destruction.[31]

2.1.4. DISTRIBUTION OF NSAIDs INTO INFLAMED AREAS:[27]

The physico-chemical properties of the acidic NSAIDs (pKa's 3-6 and high lipid solubility), as well as plasma protein binding capacity contributes to their accumulation in inflamed sites following oral administration.[32] Radio-labelled NSAIDs have been shown in animal models to be preferentially distributed into inflamed tissue.[33]

2.1.5. EVALUATION OF NSAIDs:[34]

The complexity of the inflammatory process and the diversity of the drugs that have been found effective in modifying this process has resulted in the development of numerous methods of assay capable of detecting anti-inflammatory substances.

2.1.5.1. Carrageenin paw edema in rats:[35]

This has been one of the most popular methods with pharmacologists. In this procedure, one hour after administering drugs orally , 0.1ml of 1% carrageenin is injected sub-plantar into the right hind paw. Right paw volumes (in milliliters) are measured prior to carrageenin injection using a mercury plethysmograph (i.e. zero time reading). After three hours, right paw volumes are remeasured and the % change in paw edema volume is calculated. The statistical significance of any difference is determined.

Carrageenin-induced paw edema is a classic model of non-immune based inflammation.[36] Edema in the rat paw after injection of carrageenin is the result of immediate increase in vascular permeability,[37,38] the accumulation of fluid and eventual infiltration of PMNs and monocytes.[39] The exact mechanism whereby this edema is reversed is not completely understood, although it is generally believed to involve the inhibition of prostaglandin synthesis via cyclooxygenase.

2.1.5.2. Adjuvant arthritis in rats:[35]

A suspension of *Mycobacterium butyricum* (0.5mg/0.1 ml) in light mineral oil is injected subcutaneously into the right paw of male rats. Drugs are administered orally in 0.5% methylcellulose. Paw volumes are measured by a mercury plethysmograph at the time of injection of adjuvant and after the development of inflammation. Drug effects are expressed as percentage change from controls.

2.1.5.3. Inhibition of prostaglandin synthesis:

NSAIDs have been evaluated by studying the inhibition of formation of prostaglandins from sheep seminal vesicles[40] and cell cultures.[41] Levine et al.[42] have shown that a mouse fibrosarcoma cell line in culture ($HSDM_1C_1$) synthesizes and secretes large amounts of $PGF_{2\alpha}$. This system has been used[41,42] to study the prostaglandin synthesis inhibition by indomethacin, aspirin and isoxicam. $HSDM_1C_1$ cells are seeded and grown overnight in appropriate medium.[42] The control group of cells are treated with arachidonic acid, while for the treatment group both arachidonic acid and the drug are added. After one hour the culture medium is assayed for prostaglandins by a radioimmunoassay method. Inhibition of prostaglandin formation in the treatment group is expressed as a % of control values.

A number of other tests are also used to evaluate anti-inflammatory activity of drugs. Some important ones are: reversed passive Arthus reaction in rats,[43] yeast-induced fever in rats,[35] urate-induced synovitis in dogs,[35] Arthus reaction in guinea pig knee joints[44] and the cotton pellet granuloma[45] method.

2.1.6. NSAIDs IN CLINICAL USE:

NSAIDs are a class of therapeutic agents, largely developed in the past two decades for the treatment of inflammation and pain associated with arthritis and other inflammatory conditions. Some of the drugs currently used are listed below and representative structures are shown in (Fig. 4).

1. Carboxylic acids	2. Acetic acids	3. Propionic acids
Aspirin	Indomethacin	Ibuprofen
Diflunisal	Sulindac	Naproxen
Mefenamic acid	Diclofenac	Ketoprofen
Meclofenamate	Tolmetin	Pranoprofen

4.Butyric acids	5. Acidic enols	6.Non-acidic
Bucloxic acid	Phenylbutazone	Proquazone
Fenbufen	Piroxicam	Ditazole
	Isoxicam	Tiflamizole

2.2. **Inhibition of lipoxygenase pathway:**[17]

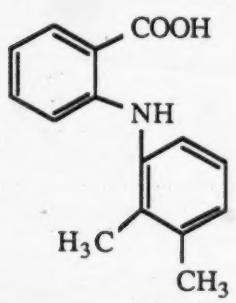
Arachidonic acid is oxidized by a number of different lipoxygenases to yield hydroperoxyeicosatetraenoic acids (HPETEs).[46] 5-Lipoxygenase, and its subsequent pathway to leukotrienes (Fig 1), has been the focus of most intensive investigation. Interest in this pathway is derived from the leukotrienes C_4, D_4 and E_4, which are primary mediators in human asthma and from leukotriene B_4, a potent chemotactic factor believed to play a role in chronic inflammation.[8]

2.2.1. SELECTIVE INHIBITORS:

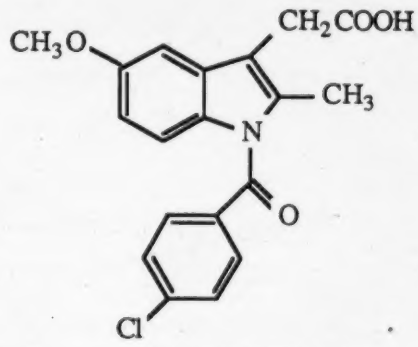
2.2.1.1. Inhibitors of 5-lipoxygenase:[47]

The development of lipoxygenase inhibitors is still at an early stage. The discovery of the link between 5-lipoxygenase and the leukotrienes dates back only to 1979.[7] Due to lack of uniformity in such factors as enzyme source, preparation and assay procedures, it is often very difficult to compare results from different studies. The different types of compounds which inhibit 5-lipoxygenase are discussed in a recent review by Salmon.[47]

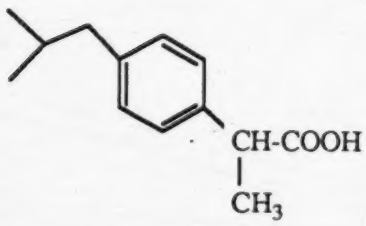
The anti-oxidant nordihydroguaiaretic acid (NDGA)[48] has been used by several investigators as a selective inhibitor of 5-lipoxygenase, although it inhibits other lipoxygenases and cyclooxygenase at higher concentrations.



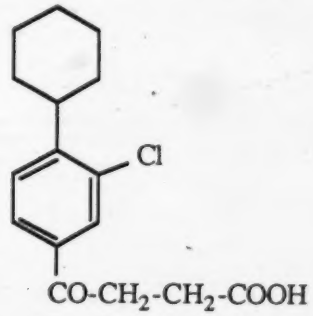
1. MEFENAMIC ACID



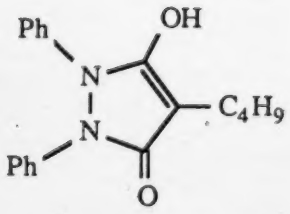
2. INDOMETHACIN



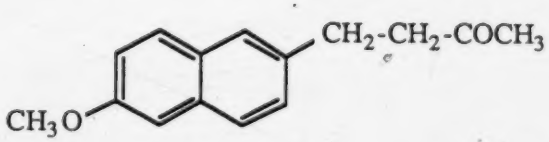
3. IBUPROFEN



4. BUCLOXIC ACID



5. PHENYL BUTAZONE



6. NABUMETONE

Fig. 4: Example of each class of NSAID.

Natural products such as flavonoids exhibit potent and relatively selective activity against 5-lipoxygenase. Quercetin, esculetin and baicalein inhibit 5-lipoxygenase and 12-lipoxygenase but not cyclooxygenase.[49] Some of these compounds are present in plant extracts which have been used for centuries in oriental medicine for treatment of inflammatory ailments. It may be that the benefits of these remedies are due to the inhibition of 5-lipoxygenase.

Nafazatrom, originally developed as an anti-thrombotic agent is a relatively selective inhibitor of 5-lipoxygenase.[50] Since nafazatrom is believed to be a reducing co-factor for peroxidase, it could act by increasing 15-HETE synthesis, which in turn may inhibit 5-lipoxygenase.[51,52]

A derivative of benzoquinone, AA861, selectively inhibits 5-lipoxygenase.[53] It has been shown to reduce allergic bronchoconstriction in guinea pigs and to reduce, moderately, carrageenin-induced paw edema and pleurisy in rats.[54]

Piriprost was reported to inhibit the generation of leukotrienes but not the formation of 12-HETE or co-products.[55] Piriprost has complex effects on eicosanoid synthesis and its precise mechanism of action is unclear.[56] Piriprost is being evaluated primarily as an inhibitor of peptido-lipid leukotrienes synthesis and therefore a potential anti-asthmatic drug.

2.2.2. NON-SELECTIVE INHIBITORS:[57]

2.2.2.1. 'Universal' inhibitor of arachidonic acid metabolism:

5, 8, 11, 14-Eicosatetraenoic acid (ETYA) is a structural analog of arachidonic acid in which all double bonds are replaced by triple bonds. This compound has been a valuable general purpose inhibitor of arachidonic acid metabolism.[58] Although assumption has often been made that it is a dual inhibitor of both the cyclooxygenase and lipoxygenase pathways, its actions are more complex. For example, doses that block both cyclooxygenase and 5-lipoxygenase have been reported not to affect 12-lipoxygenase.[59] In

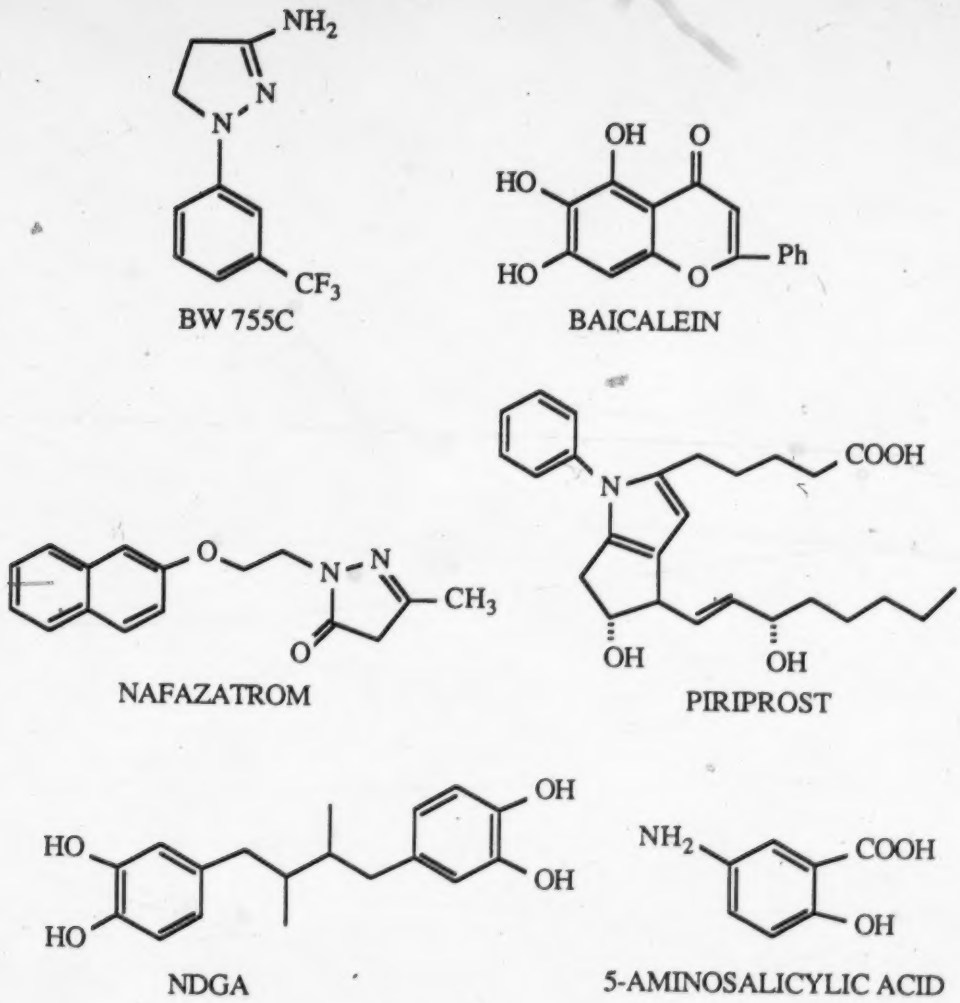


Fig. 5: Structures of some compounds which inhibit leukotrienes synthesis.

other reports doses that inhibited prostaglandin production did not affect SRS-A formation.[60]

2.2.2.2. Inhibitors affecting both cyclooxygenase and 5-lipoxygenase (Dual inhibitors):

Important among compounds that have a dual action are phenidone,[61] BW 755C (3-amino-1-[m-trifluoromethylphenyl]-2-pyrazoline) and analogs thereof,[62] and benoxaprofen.[63] In general these compounds appear to be equipotent in inhibiting cyclooxygenase and 5-lipoxygenase. BW755C (although no longer pursued in clinical

trials, due to toxicity) has become more or less the literature standard for dual activity, having shown activity *in vivo*,[64,65] on tracheal smooth muscle[66] and on sensitized perfused guinea pig lung.[67]

As can be seen from Fig.5, structurally diverse compounds have been shown to inhibit the lipoxygenase pathway. Therefore few generalizations concerning structure activity can be drawn. This clearly attests to the molecular heterogeneity of leukotriene receptors, as supported by experimental evidence.[68]

2.2.2.2.1. Therapeutic potential of dual inhibitors:[69]

The therapeutic potential of inhibiting lipoxygenase as well as cyclooxygenase depends upon the contribution of leukotrienes to the development of the disease process. Since their discovery some 40 years ago, the SRSs (now shown to be peptido-lipid leukotrienes) have been thought to play an important part in immediate hypersensitivity responses.[70] There is increasing evidence that leukotrienes are involved in inflammatory responses.[10,11]

Therefore a general concept that compounds capable of inhibiting both cyclooxygenase and lipoxygenase may possess greater anti-inflammatory activity, attracted much interest.[69] The dual inhibitors would inhibit both the formation of prostaglandins and migration of white blood cells to the site of inflammation. This would lead to more effective anti-inflammatory action. Dual inhibitors should have similar properties to the anti-inflammatory corticosteroids, which reduce prostaglandin and leukotriene production by preventing the release of arachidonic acid from phospholipids.[71] This activity explains why steroids are better anti-inflammatory drugs than NSAIDs and why they are effective in diseases like asthma, while selective inhibitors of cyclooxygenase are not. Despite their superior therapeutic actions, there are many unacceptable side effects associated with corticosteroids. It is possible that dual inhibitors will have steroid-like therapeutic activity, but be free from steroid related toxicity.

2.3. EVALULATION OF INHIBITORS OF 5-LIPOXYGENASE:[72]

2.3.1. *In vitro* models:

Several *in vitro* procedures for assessing the inhibition of 5-lipoxygenase have been reported. Most involve monitoring the conversion of exogenous [^{14}C] arachidonic acid to 5-HETE and/or LTB_4 by cells stimulated with the calcium ionophore A23187. PMNs from different species and also various cell lines have been employed. Several putative inhibitors have been evaluated using a partially purified enzyme from PMN.[73]

A specific radioimmunoassay for LTB_4[74] allows rapid assessment of low levels of the compound without prior extraction or chromatography. The sensitivity of radioimmuno assay allows stimuli more physiologically relevant (e.g. opsonized zymosan) than A23187 to be used to induce metabolism of endogenous arachidonic acid by 5-lipoxygenase.

Guinea pig spirally cut trachea and lung parenchyma strips have been used to screen potential 5-lipoxygenase inhibitors and/or leukotriene receptor antagonists.[75] Arachidonic acid, when administered to guinea pig isolated trachea in the presence of indomethacin induces pronounced contraction of smooth muscle. This has been shown to be due to synthesis and activity of peptido-lipid leukotrienes. Therefore if the test substance inhibits arachidonic acid induced contractions of indomethacin-treated trachea, it means that the substance is inhibiting the lipoxygenase pathway or blocking the receptor site of leukotrienes (section 7.0.).

2.3.2. *In vivo* models:

Although there are many compounds which inhibit 5-lipoxygenase *in vitro*, there are few reports of *in vivo* activity. Many of the compounds which are active *in vitro* have very short half-lives *in vivo*. The potent inhibitory activities exhibited *in vitro* by ETYA and NDGA have not been confirmed *in vivo* .[76]

Salmon et al.[77] studied the effects of several compounds on the synthesis of LTB_4, cyclooxygenase products and PMN accumulation in rats. BW755C (a dual inhibitor)

reduced the concentrations of LTB_4 and the cell count. Leukocyte accumulation was also inhibited by NSAIDs indomethacin and flurbiprofen. Although these drugs reduced the concentrations of both PGE_2 and TXB_2 in the exudate, they did not affect LTB_4 levels. This data suggests that reduction of PMN accumulation by NSAIDs is mediated by a mechanism other than inhibition of LTB_4 synthesis.

The activity of 5-lipoxygenase inhibitors in animal models of asthma has been examined. It has been demonstrated that BW755C reduces anaphylactic bronchoconstriction in guinea pigs[67] and monkeys.[78]

2.4. INTERACTION OF CYCLOOXYGENASE AND LIPOXYGENASE PATHWAYS:

The possible shunting of the common substrate, arachidonic acid from cyclooxygenase pathway to lipoxygenase pathway when the former is blocked by inhibitors like NSAIDs has been demonstrated.[17] Recently more complex interactions, both stimulatory and inhibitory, between the two pathways via their metabolites have also been noted. For example, LTB_4 can stimulate the cyclooxygenase pathway, possibly via its effect on phospholipase, to increase the availability of free arachidonic acid from membrane phospholipids. Conversely PGE_2 and PGI_2 can inhibit the production of leukotrienes by human PMN and rat peritoneal macrophages.[79] The overall *in vivo* effect of inhibition of individual pathways in the arachidonic acid cascade is likely to be a highly complex and dynamic one.

2.5 DRUG DEVELOPMENT POTENTIAL:

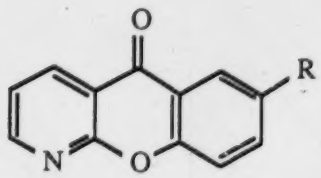
The various physiological roles of prostaglandins and leukotrienes and their involvement in various diseases, opens up a vast area for exploring the development of new drugs. At present only one step in the arachidonic acid cascade has been fully exploited in the development of non-steroidal anti-inflammatory drugs. They are currently among the best selling pharmaceutical products, accounting for over 4.5% of the world pharmaceutical market.[8] It is the success of these drugs based on the inhibition of one

enzyme in the arachidonic acid cascade that has led to intense research efforts into new drugs, particularly inhibitors of lipoxygenase.

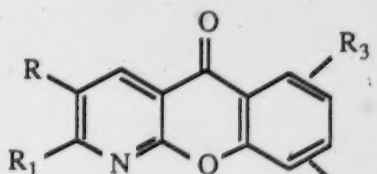
3.0. INTRODUCTION TO AZAXANTHONES:

3.1. **Pharmacology of 1-azaxanthones:**

The patent literature contains a number of references to 1-azaxanthones (5H-[1]-benzopyrano[2,3-b]pyridin-5-one) possessing a wide variety of pharmacological properties. However detailed pharmacological data is not readily available.



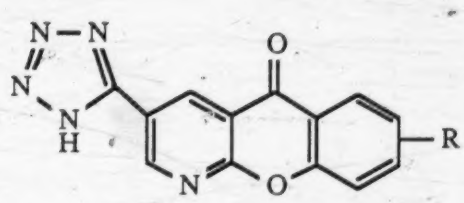
(1)



(2)

Substitution at C-7 position of (1) with aldehyde, carboxylic acid, ester and various other substituents (including hydroxyalkyl, aminoalkyl and alkoxyalkyl) gave compounds with anti-allergic, anti-inflammatory and diuretic activity.[80-84]

Numerous other benzopyranopyridinones (2) (R=H, CN, COOH; R_1=alkyl, aryl, COOH, OH, alkoxy, NH_2, alkylamino; R_2, R_3= H, alkyl, alkoxy, halogen, NO_2, OH, COOH, CN, CHO, alkylcarbonyl) have been reported to possess anti-allergic, anti-asthmatic and bronchodilator activity.[85-91]



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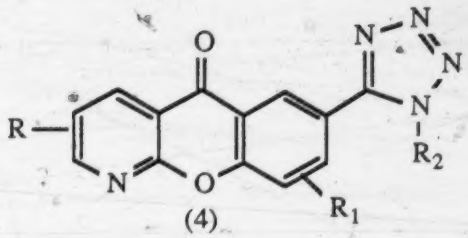
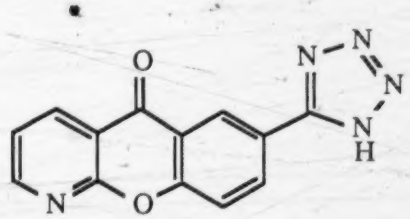


(4)

The tetrazolyl substituent when present on either the pyridine ring or the benzene ring confers excellent anti-allergenic activity. Thus compounds (3) (R=H, alkyl, alkoxy, halogen, NO_2, COOH, OH, alkylamino) have been reported to possess bronchodilator and anti-allergic activity.[92,93] Similarly the tetrazolyl compounds (4) (R=H, Ph, substituted Ph, halogen, alkoxy, alkyl; R_1= Me, Cl, OMe, H; R_2=H, Me, allyl, vinyl, CH_2COOH, $Me_2NCH_2CH_2$, hydroxyalkyl and others) have shown anti-allergic, anti-asthmatic, anti-histaminic, anti-inflammatory and anti-diuretic activity.[94-98]

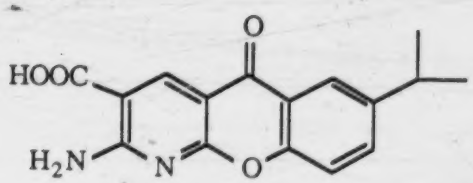


(5)

Compound (5) traxanox, is the most active in the above series. It is orally active at a dose of 2.5mg/kg in the rat passive cutaneous anaphylaxis (PCA) test. It is also five times as active as disodium chromoglycate (DSCG).[99,100] DSCG, used since 1968, is of value as a prophylactic medication for chronic asthma. It acts by blocking the release of chemical mediators of type I hypersensitivity reactions. Effect of (5) has been studied extensively on type I-IV allergic reactions.[101] Traxanox dose dependently inhibited experimentally induced 48 hr PCA, in rats in doses of 1-10 mg/kg orally and 0.1-0.5 mg/kg intravenously. Also passive anaphylactic bronchoconstriction was inhibited in doses of

0.025-0.1mg/kg intravenously. Pharmacological screening tests showed that at anti-allergic doses traxanox had little effect on the other major systems and organs.[103]

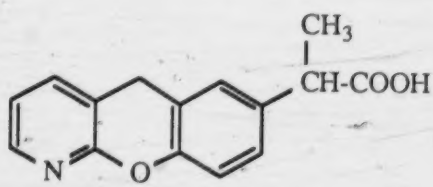
A number of analogs of 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acids were synthesized and their anti-allergic activity have been studied extensively.[104,105]



(6)

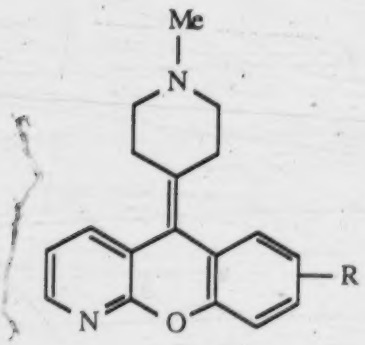
Compound (6) was the most promising in this series. It inhibited immunologically-stimulated and LTD_4 -induced bronchoconstriction in laboratory animals. Like DSCG it inhibits rat IgE-mediated PCA and histamine release from rat peritoneal mast cells. Anti-allergy action of this compound seems to be associated with inhibition of chemical mediator release and antagonistic activity on SRS-A.[106]

A series of benzopyranopyridinyl acetic acid and propionic acid derivatives have been synthesised by various methods and the relationship between their structure and anti-inflammatory activity was assayed by the method of ultraviolet erythema. It was found that 2-(5H-[1]benzopyrano-[2,3-b]pyridin-7-yl)propionic acid had the most potent anti-inflammatory activity.[107] This compound (7) is now marketed under the name pranoprofen.



(7)

A number of azaxanthenes (8) were examined for bronchodilating and anti-histaminic activity[108] in guinea pigs after an oral dose of 30mg/kg. Of considerable interest



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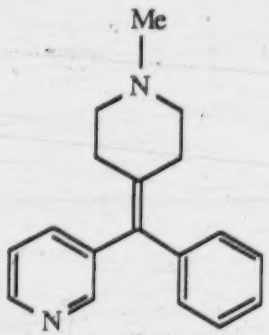
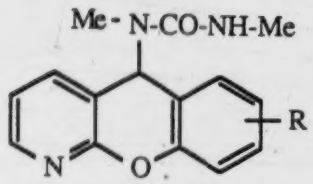


(9)

in this series of compounds is the pharmacological activity of (8) R = H, maleate. This compound shows the profile of a combined potent bronchodilator and moderate anti-histaminic agent. It causes the relaxation of the bronchospasm induced by anaphylaxis in the isolated perfused lung and protects against histamine both *in vitro* and *in vivo* . Aromatic ring substitution { (8), R = Cl, F, Me, OMe, t-Bu} did not enhance the activity except with 7-F compound. It appears that the conformational rigidity of compound (8) is essential for activity. Compound (9), lacking the heteroatom bridge, was found to be inactive at an oral dose of 30 mg/kg in guinea pigs.

A 1981 report[109] described the antisecretory and anti-ulcer activity of benzopyranopyridinyl-1,3-dimethylureas (10), { R= H, CF_3, F, Me, Cl, NO_2, OMe, CH_2OH} and benzopyranopyridinylureas (11), {R=H, Me; R_1=NH_2, N,N-dialkyl, morpholino, piperazino, piperidino }. A number of these compounds possessed anti-secretory activity comparable to cimetidine. However, unlike cimetidine, these agents were



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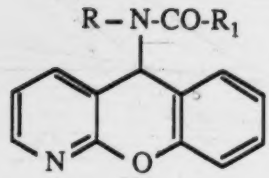
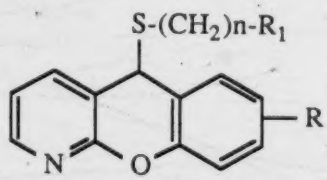


(11)

more active after intravenous rather than oral administration. The authors state that oral activity was observed with higher doses. Compound (11), { R=Me; R_1=morpholino} was the most active compound in the benzopyranopyridinylurea series (11). It was pointed out that while derivatives (10) and (11) inhibited histamine-stimulated gastric acid secretion, they were not histamine H_2 receptor antagonists.[109]

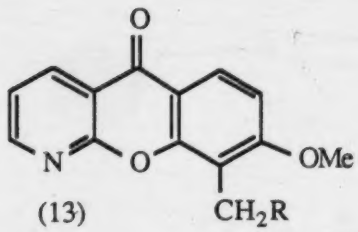
The 5-[(aminoalkyl)thio]benzopyranopyridines (12),{R=H, OMe; R_1=NH_2, morpholino, piperidino; n=2 or 3} gave good anti-secretory activity in rat and dog. As with



(12)

compounds (10) and (11) the best activity was produced after intravenous administration and did not appear related to anti-cholinergic effects or histamine H_2-receptor antagonism.[110]

1-Azaxanthones (13), {R=NMe_2, NEt_2, N-piperidino, N-morpholino} and (14), {R_1=H, Me; R_2, R_3=H, halogen, Me, Ph, OMe; X=alkylidene} had analeptic[111] and pote-



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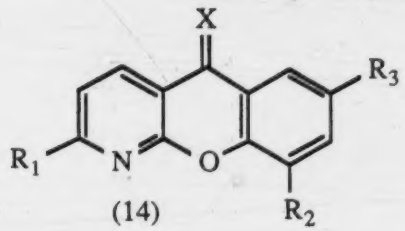
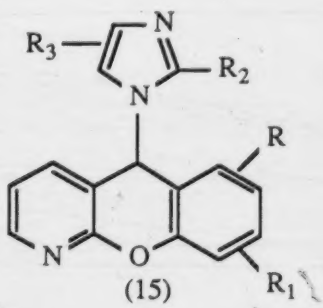


(14)

ntial CNS activity,[112] respectively.

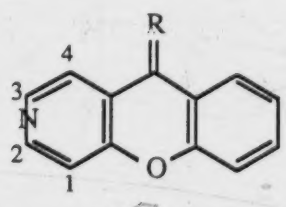
Benzopyranopyridinylimidazoles (15) {R, R_1=H, haloalkyl, alkoxy, NO_2, cyano, alkoxy carbonyl, methyltetrazolyl; R_2, R_3=H, alkyl, Ph; showed antiulcer activity at 30mg/kg, orally in rats.[113]



(15)

3.2. **Pharmacology of 2,3 and 4-azaxanthones:**

A number of aminoalkyl derivatives of 2,3 and 4-azaxanthones have been studied for anti-histaminic and bronchodilator activities.[108] It was generally observed that these compounds showed less activity and more toxicity as compared to the 1-azaxanthone series.[108]

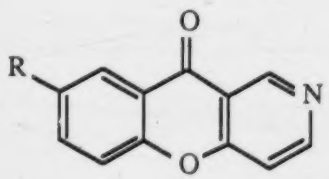


R= 4-$C_6H_{11}N$, 4-$C_7H_{13}N$
4-$C_8H_{15}N$, 4-$C_{12}H_{15}N$

(16)

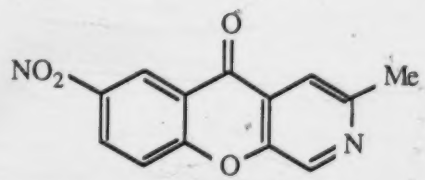
The 2, 3 and 4-aza analogs of (16) in which a 3-quinuclidylidene was present at C-5 were also synthesized.[114] Although these compounds were orally active anti-histaminic and bronchodilating agents (guinea pig), in general they possessed greater toxicity than the corresponding piperidylidene analogs.

A number of 2 or 3-azaxanthenyl acetic, propionic acid and carboxylic acid derivatives have been studied for anti-inflammatory activity. Their activities were not greater than the corresponding 1-azaxanthone analogs. Detailed pharmacological results were not presented.[115,116]



(17)

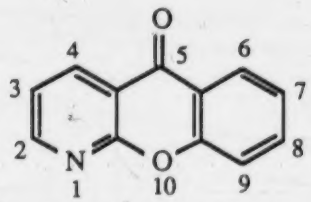
Compounds (17) { R=tetrazol-5-yl, $CONH_2$, CN, COOH } showed anti-allergic and anti-tumor activity.[117]



(18)

Compound (18) prepared by the direct cyclization of corresponding substituted phenoxyisonicotinate, was reported to be an antibacterial.[118]

3.3. Chemistry of 1-azaxanthones:



(19)

5H-[1]Benzopyrano[2,3-b]pyridin-5-one (1-Azaxanthone)

3.3.1. SYNTHETIC ROUTES:

1-Azaxanthones can be prepared[108,118] in high yields by the intramolecular cyclization of the corresponding phenoxypyridine acid (22) using polyphosphoric acid. The phenoxypyridine acid itself is made by the condensation of 2-chloronicotinic acid (20) with phenol (21) (Fig. 6).

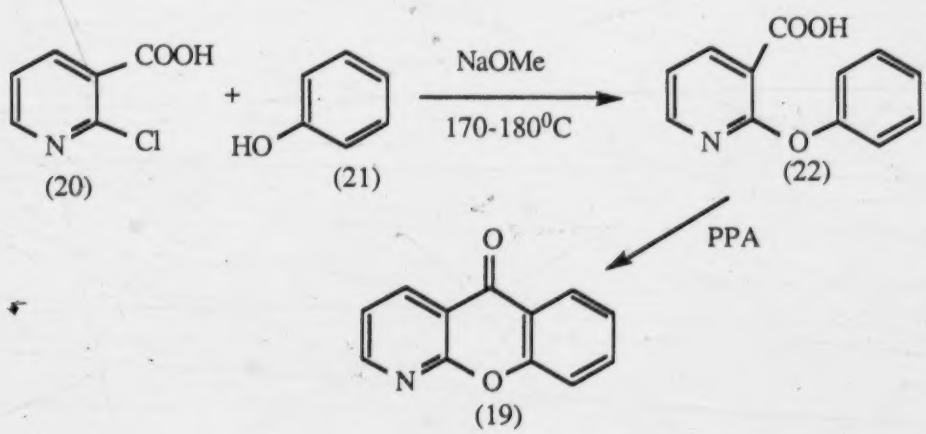


Fig. 6: Synthesis of 5H-[1]benzopyrano[2,3-b]pyridin-5-one.

When a para-substituted phenoxypyridine acid was used, PPA was the reagent of choice and gave excellent yields of 7-substituted 1-azaxanthones. When a meta-substituted phenoxypyridine acid was cyclised using the same reagent it gave a mixture of 6-and 8-substituted 1-azaxanthones (Fig. 7).

It has been found that the use of aluminum chloride in carbon disulphide on the meta-substituted phenoxypyridine sterically directs the orientation so that only the 8-substituted azaxanthone is formed (Fig. 7).[119]

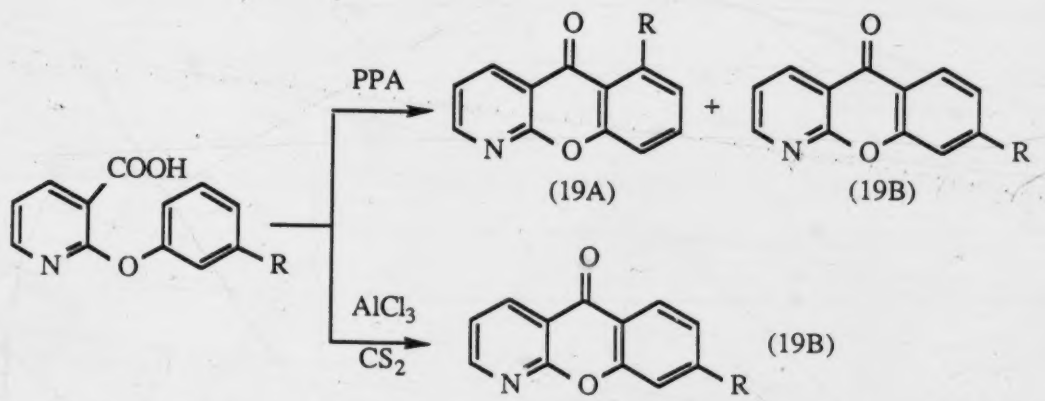


Fig. 7: Reaction of phenoxypyridine acid with PPA or $AlCl_3$.

A method for the synthesis of 3-cyano, 3-alkoxycarbonyl and 3-formyl-1-azaxanthone derivatives has been reported.[120] They were prepared by the reactions of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehydes (23) with acetylene derivatives or with reactive methylene compounds as shown in (Fig. 8).

3-Acetyl-2-methyl-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine (28) was obtained in 80% yield by the condensation of 4-oxo-4H[1]benzopyran-3-carbonitrile with acetylacetone.[121] The mechanism of this condensation is shown in Fig.9.

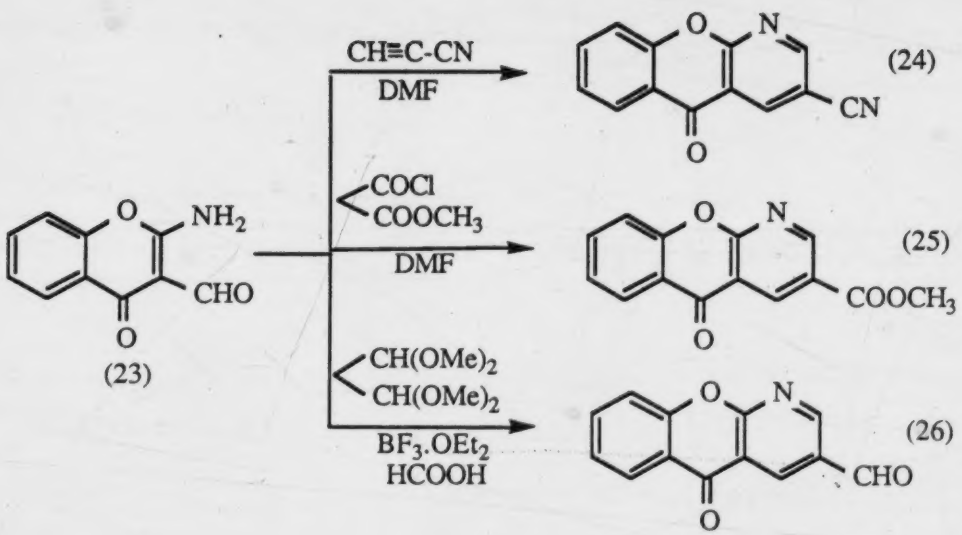


Fig.8: Synthesis of 3-substituted 1-azaxanthones.

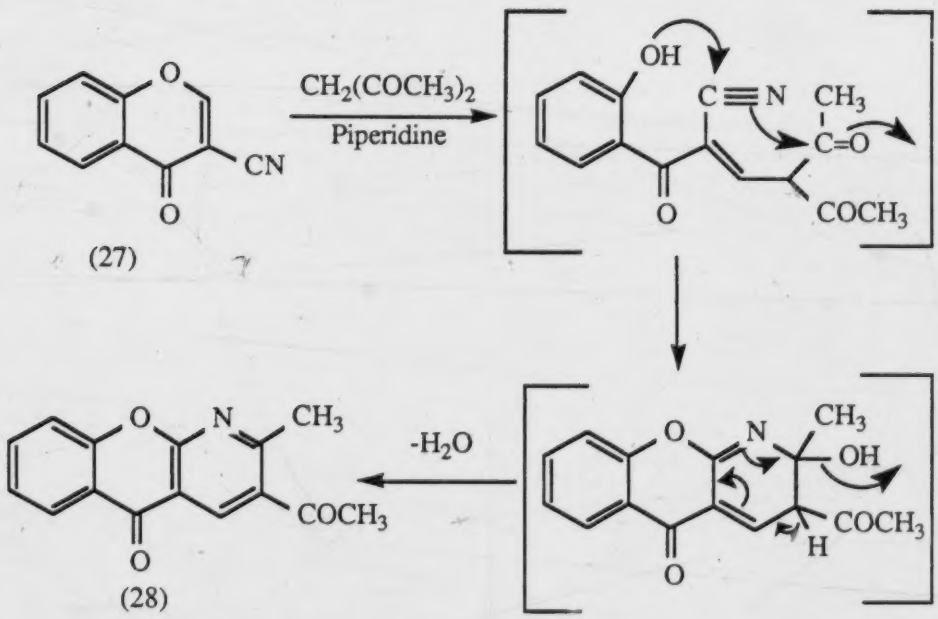


Fig. 9: Mechanism of formation of 3-acetyl-2methyl-1-azaxanthone.

Reaction of 6-methyl-2-phenoxynicotinonitrile with p-substituted phenylmagnesium bromides gave 6-methyl-2-phenoxy-3-aroylpyridines.[122] These were then cyclised to 5-

hydroxy-5-arylbenzopyrano[2,3-b]pyridines by treating with concentrated sulfuric acid in glacial acetic acid (Fig.10).

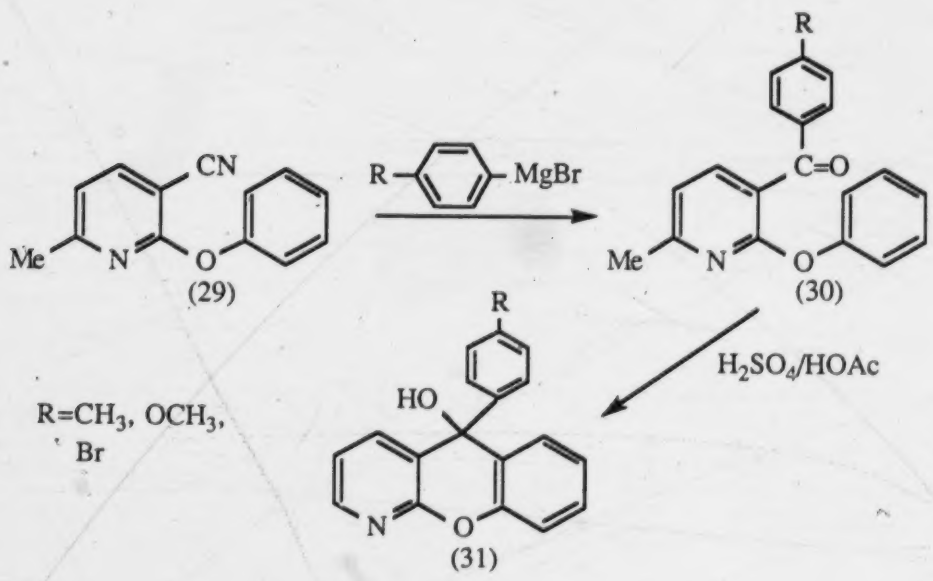


Fig. 10: Synthesis of 5-hydroxy-5-aryl-1-azaxanthone.

3.3.2. REACTIONS OF 1-AZAXANTHONES:

3.3.2.1. Reactions at the C-5 position:

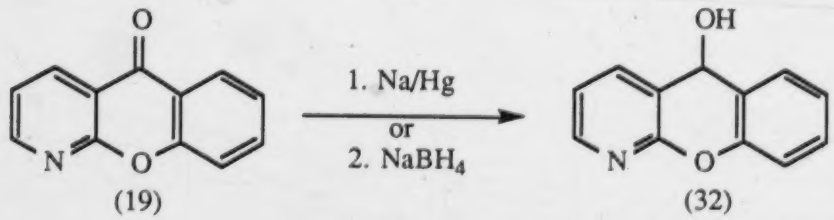


Fig. 11: Reduction of 1-azaxanthone.

Reduction of the C-5 ketone group has been accomplished by refluxing with sodium and mercury in ethanol[123] or using sodium borohydride in methanol[109] at room temperature (Fig.11).

Further reduction of the 5H-[1]benzopyrano[2,3-b]pyridin-5-ol (32) to the 5H-[1]benzopyrano[2,3-b]pyridine can be done by refluxing (32) with a 20% mixture of hydrochloric acid in isopropyl alcohol (Fig.12).[124]

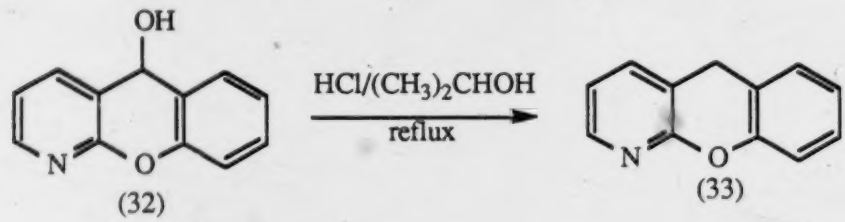


Fig.12 : Reduction of 1-azaxanthene-5-ol.

The alcohol (32) when treated with 1,3-dimethyl urea in a mixture of glacial acetic acid and acetonitrile at reflux gave 1-(benzopyranopyridin-5-yl) -1,3-dimethyl urea (34) (Fig. 13).

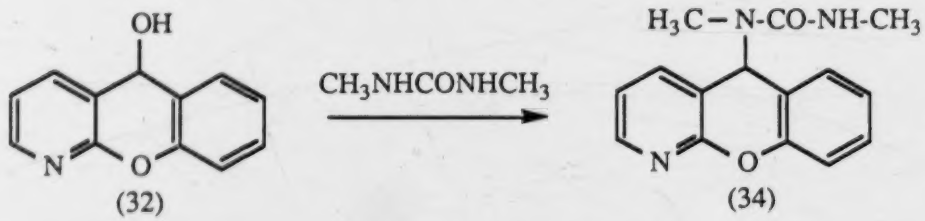


Fig. 13: Reaction of 1-azaxanthene-5-ol with 1,3-dimethylurea.

A similar reaction of the alcohol (32) with (dimethylamino)alkylthiols gives 5-[(aminoalkyl)thio]-5H-[1]benzopyrano[2,3-b]pyridines (Fig. 14).[110]

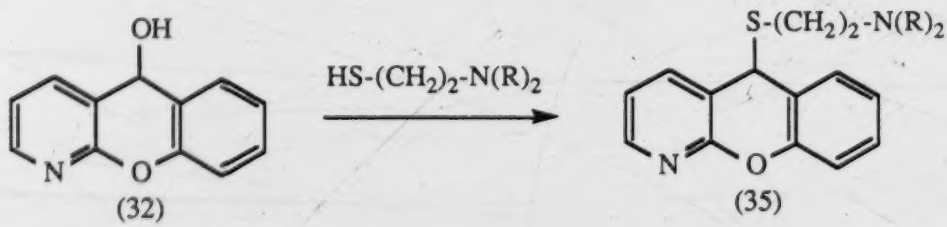


Fig. 14: Reaction of 1-azaxanthene-5-ol with (dialkylamino)alkylthiols.

3.3.2.2. Reactions with Grignard reagents:

Three different products are formed in the reaction of Grignard reagents with 1-azaxanthones.[125] The formation of 4-substituted-1,4-dihydroazaxanthone (36), 5-substituted-5-hydroxy-1-azaxanthene (37) and 4,5-disubstituted-1-azaxanthenes (38) is dependent on the solvent used in the preparation of the Grignard reagent (i.e. ether or THF), the steric properties of the reagent and on the temperature.

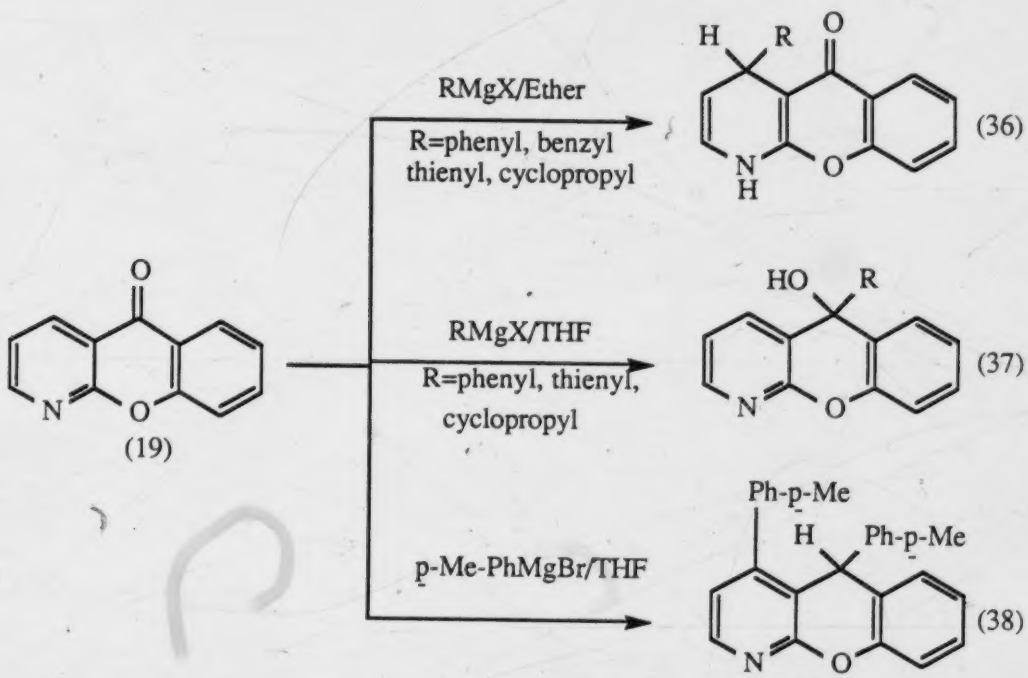


Fig. 15: Reaction of 1-azaxanthone with grignard reagents.

Aromatic type Grignard reagents which incorporate phenyl, benzyl, and thienyl groups or highly strained cyclopropyl or bulky cyclohexyl moities gave 4-substituted 1,4-dihydro-1-azaxanthones (36), when the reagents are prepared in ether. These dihydropyridines can be oxidized by dehydrogenation with chloranil, to the corresponding 4-substituted-1-azaxanthones (Fig. 15).[125]

When the reaction is conducted in THF, attack generally occurs at the C-5 carbonyl, leading to products of type (37). Reaction of p-methylphenylmagnesium bromide in THF resulted in the isolation of a third type of reaction product (38).

Reaction of 1-azaxanthone with 4-chloro-1-methylpiperidine was done by reductive alkylation with sodium in liquid ammonia or by means of a Grignard reagent (Fig. 16).[102]

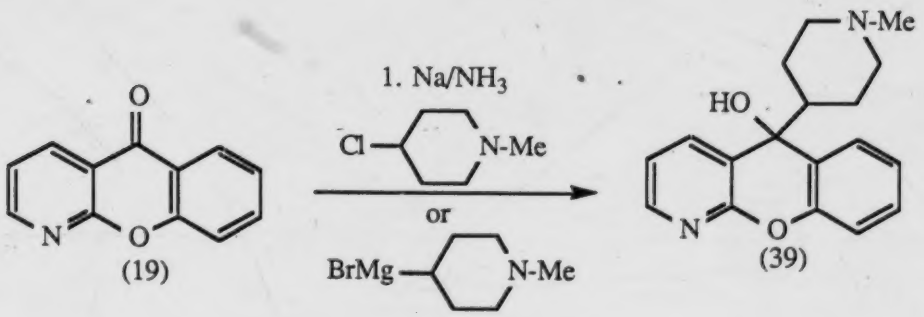


Fig.16: Preparation of 5-hydroxy-5-(1-methyl-4-piperidyl)-1-azaxanthene.

3.3.2.3. Reactions with alkali hydroxide:

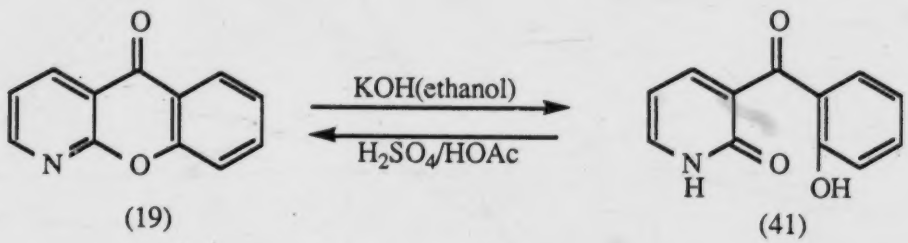


Fig. 17: Reaction of 1-azaxanthone with a base.

Heating 1-azaxanthone with an aqueous alcoholic solution of potassium hydroxide results in cleavage of the pyranone ring to give 3-(o-hydroxybenzoyl)-2-pyridinone (41). The pyridone is cyclised back to 1-azaxanthone in 73% yield when it is heated in glacial acetic acid in the presence of sulfuric acid (Fig. 17).[126]

1-Azaxanthone does not form an oxime when heated with hydroxylamine hydrochloride in pyridine and ethanol.[127] Under forcing conditions, with excess of potassium hydroxide in ethanol, 1-azaxanthone reacted with hydroxylamine hydrochloride to give a mixture of two products, 3-(2-1H-pyridinon-3-yl)-1,2-benzisoxozole (43) and 3-o-hydroxyphenyl(2-1H-pyridinon-3yl)ketoxime (42) (Fig. 18).

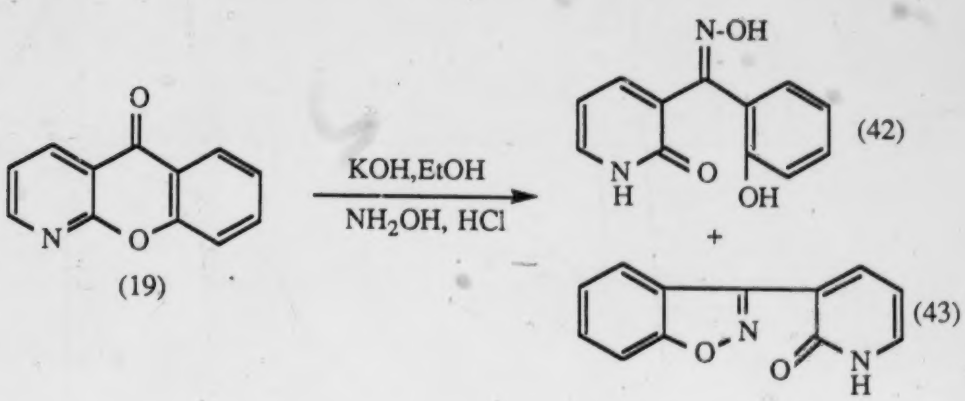


Fig. 18: Reaction of 1-azaxanthone with hydroxylamine.

3.3.2.4. Electrophilic aromatic substitution reactions:

Nitration of 1-azaxanthone under standard conditions (KNO_3/H_2SO_4) leads to the exclusive formation of 7-nitro-1-azaxanthone.[108] 1-Azaxanthone is not acylated by Friedel-Crafts reaction, although 1-azaxanthene reacts under similar conditions.[85]

Chloromethylation of 8-methoxy-1-azaxanthone (44) gives 8-methoxy-9-chloromethyl-1-azaxanthone (45) from which centrally acting 1-azaxanthone derivatives have been synthesised[111] by reaction with dialkylamines (Fig. 19).

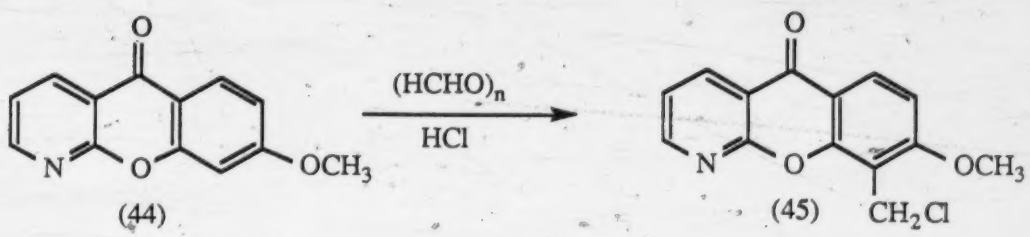


Fig. 19: Chloromethylation of 8-methoxy-1-azaxanthone.

Chloromethylation of 1-azaxanthene leads to 7-chloromethyl-1-azaxanthene. This reaction has been used to synthesize 7-acetic acid and propionic acid derivatives of 1-azaxanthene (Fig. 20).[128]

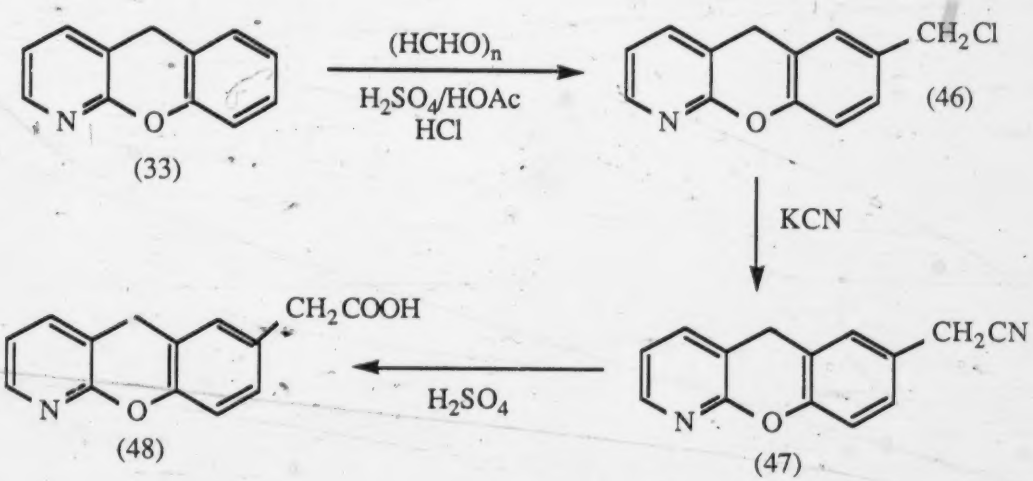


Fig. 20: Synthesis of 5H-[1]benzopyrano[2,3-b]pyridin-7-yl-acetic acid.

3.3.2.5. Hydrogenation reaction:

Hydrogenation (Raney nickel, 50 atm.pressure, 70-80^{0}C) of 1-azaxanthones leads to 1,2,3,4-tetrahydro-1-azaxanthones in 50% yields (Fig. 21).[112]

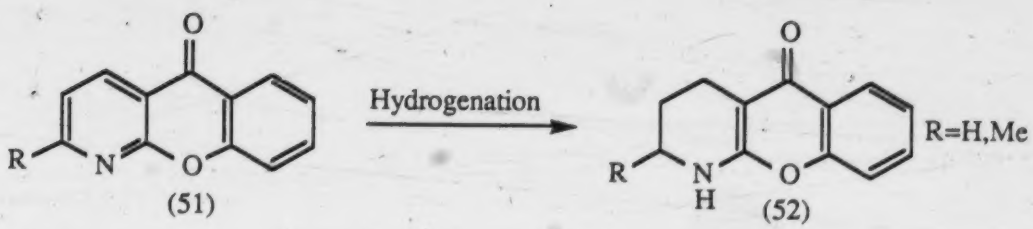


Fig. 21: Hydrogenation reaction of 1-azaxanthone.

3.4. **Physical properties of 1-azaxanthones:**

3.4.1. UV Spectra:

The UV spectra of 1-azaxanthones have been studied in detail.[126] Maxima are observed in the UV spectrum of a hexane solution of 1-azaxanthone at 225, 236, 260, 282 and 336 nm. These are due to $\pi - \pi^*$ transitions and, in contrast to the spectrum of xanthone, are of high intensity.

A decrease in the intensity of absorption maximum, which is more strongly expressed for the short-wave band and is only slight for the long wave band, is observed in the spectra of sulfuric acid solutions of 1-azaxanthone.

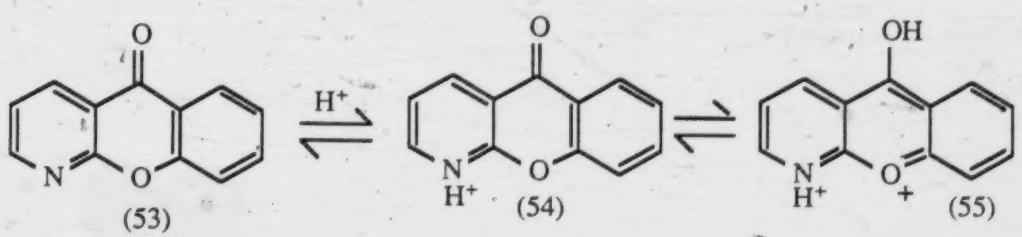


Fig. 22: Protonation of pyridine and carbonyl group of 1-azaxanthone.

This change is probably due to the formation of ion (54) preceding the protonation of the carbonyl group (55) (Fig. 22). The decrease in the pKa value of 1-azaxanthone [pKa= -9.09] as compared with the pKa of xanthone [pKa= -4.08] is associated with the manifestation of electron acceptor properties on the part of the protonated pyridine ring.

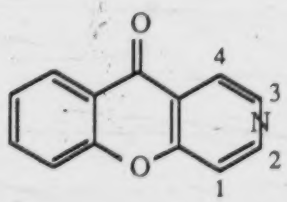
3.4.2. Infrared spectra:

The carbonyl stretching absorption of 1-azaxanthone is at 1672 cm^{-1}. It also gives absorptions at 1620, 1600, 1580 and 1570 cm^{-1} due to the stretching vibrations of the benzene (C=C) and heterocyclic rings (C=N).

3.4.3. NMR Spectra:

The ^1H nmr spectrum (δ) of 1-azaxanthone exhibits two doublet of doublets (dd) at 8.80 (J= 5.25 & 2.40 Hz) and 8.74 (J=7.74 & 2.40 Hz) due to C_2 and C_4 pyridine hydrogens respectively. The dd at 8.34 (J=7.88, 2.62) is assigned to the C_6 hydrogen. The downfield chemical shift of this hydrogen is attributed to the anisotropic effect of the C_5 carbonyl. C_8-H coupled to C_7, C_9 and C_6-hydrogens appears as a multiplet at 7.82. The doublet at 7.65 (J=7.88 Hz) is due to C_9-H. The two proton multiplet at 7.48 is due to C_3-H and C_7-H.

3.5. Chemistry of 2,3 and 4-azaxanthones:



N=2, 5H-[1]benzopyrano[2,3-c]pyridin-5-one

N=3, 10H-[1]benzopyrano[3,2-c]pyridin-10-one

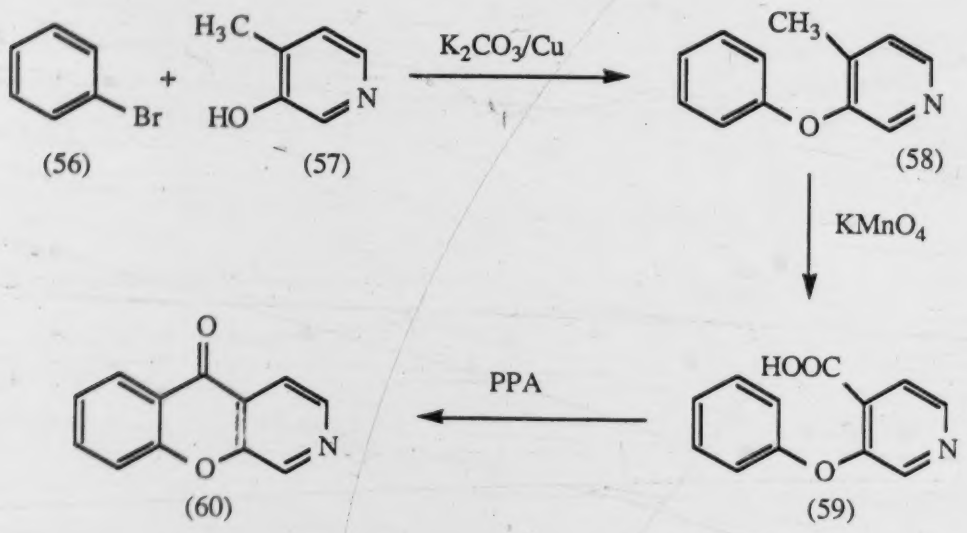
N=4, 10H-[1]benzopyrano[3,2-b]pyridin-10-one

3.5.1. Synthetic route to 2-azaxanthone:

Compared to 1-azaxanthone the synthetic routes to 2,3, and 4-azaxanthones are not straightforward. They usually involve more steps and the yields obtained are poor.

3-Phenoxy-4-picoline(58) was obtained[108] by the Ullman condensation of 3-hydroxy-4-picoline (57) and bromobenzene (56). It was then oxidised to 3-phenoxy-

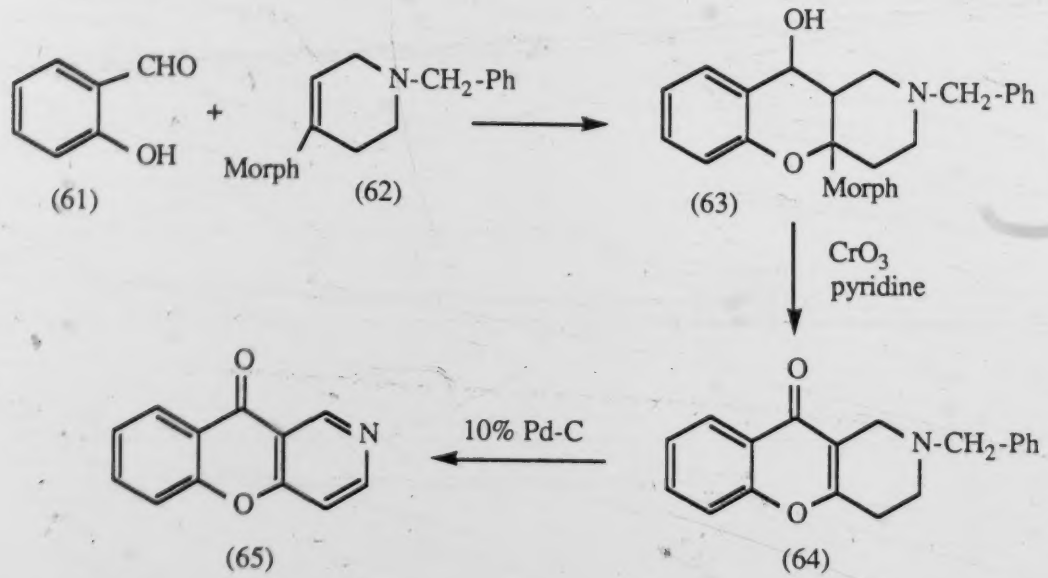
isonicotinic acid (59) using potassium permanganate and cyclised to 2-azaxanthone (60) using polyphosphoric acid (Fig. 23).



(56) (57) (58) (59) (60)

Fig. 23: Synthesis of 2-azaxanthone.

3.5.2. Synthetic routes to 3 and 4-azaxanthones:



(61) (62) (63) (64) (65)

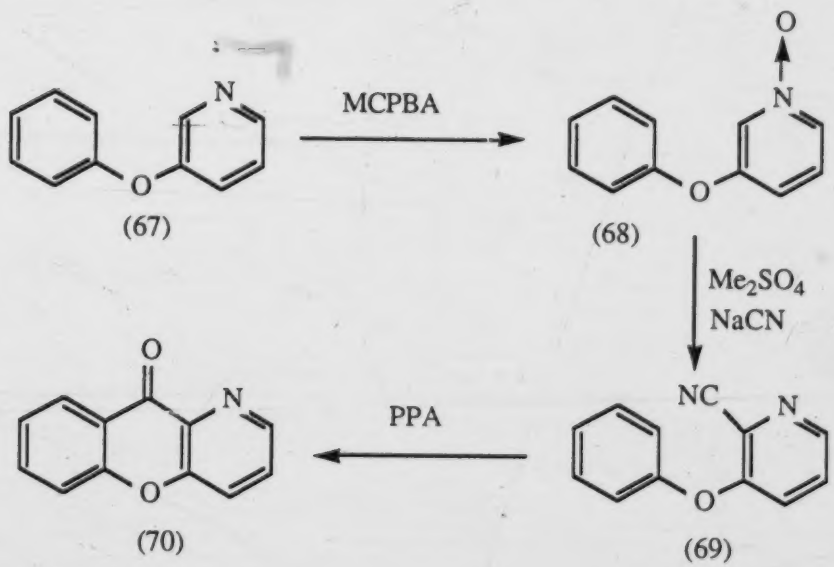
Fig. 24: Synthesis of 3-azaxanthone.

3-Azaxanthone has been prepared[129] by the condensation of the morpholine enamine of 1-benzyl-4-piperidone with salicylaldehyde. The carbinol intermediate (63) is not isolated, but directly oxidised with chromium trioxide - pyridine to the 4-pyrone structure (64) . It was then debenzylated and aromatised by refluxing in xylene in the presence of 10% palladium-charcoal (Fig. 24).

Conversion of 3-azaxanthone to 3-azaxanthene was carried out by lithium aluminium hydride reduction of (65)

(65) (66)

Fig. 25: Conversion of 3-azaxanthone to 3-azaxanthene.



(67) (68) (70) (69)

Fig. 26: Synthesis of 4-azaxanthone.

The synthetic scheme for 4-azaxanthone is summarized in Fig. 26.[108] 3-Phenoxypyridine (67) was obtained in 59% yield by heating 3-bromopyridine and phenol at 230^0 C. The N-oxide (68) obtained by MCPBA oxidation was converted into the 2-cyano derivative (69) using dimethyl sulfate and sodium cyanide. Ring closure using polyphosphoric acid gives 4-azaxanthone (70) in excellent yield.

II. OBJECTIVES OF RESEARCH

Arachidonic acid is metabolised via the cyclooxygenase and lipoxygenase pathways, to yield prostaglandins and leukotrienes, respectively. The prostaglandins are the target of an important class of agents, the NSAIDs. The leukotrienes were discovered recently (1979).[7] Their involvement in inflammation and various diseases, for example, asthma, allergy, rheumatoid arthritis and psoriasis have been fully documented.[10,11] The various physiological roles of leukotrienes and their manipulation, opens up a vast area for new product development. It has been suggested that compounds inhibiting both cyclooxygenase and lipoxygenase pathways will constitute a new class of potent anti-inflammatory drugs.[69]

In view of the pharmacological activities of azaxanthones (section 3.1.), (especially their antiasthmatic, anti-inflammatory and bronchodilatory properties) it was desirable to further explore the development of lipoxygenase and/or dual inhibitors, which incorporate the azaxanthone structure. 1-Azaxanthone derivatives were chosen since they were pharmacologically more attractive than 2,3 or 4-azaxanthones. In addition, the 1-azaxanthone nucleus can be obtained in high yield, requiring only a few steps.[108] It also possesses some of the basic requirements for cyclooxygenase inhibition, for example, hydrophobicity and a non-planar arrangement of aromatic rings. 1-Azaxanthone derivatives also satisfy the Appleton, anti-inflammatory receptor model[21] which allows considerable substituent variation, while retaining a conformationally rigid bicyclic or tricyclic system.

We envisaged modification of the 1-azaxanthone molecule at four sites ; the C-5 carbonyl, the heteroatom (O) bridge, the pyridine ring and the benzene ring. Reduction of the C-5 carbonyl to the methylene group would give 1-azaxanthene analogs. Propionic acid and acetic acid derivatives of 1-azaxanthene have been shown to possess excellent anti-inflammatory activity.[107] Reduction of the pyridine ring would lead to dihydro or tetrahydro pyridines. Structurally related compounds with reduced pyridines have shown

antiallergic properties.[132] Ring opening at the oxygen bridge would lead to loss of conformational rigidity of the tricyclic system and such compounds are expected to be inactive.[105,108] The benzene ring would constitute a major site for modification, since compounds with a wide variety of substituents on this ring are known to possess anti-inflammatory and antiallergic activity.[81-85]

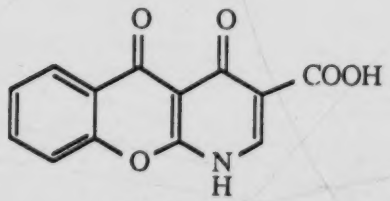
Initial pharmacological results revealed that nitrogen containing substituents on the benzene ring would provide potential lipoxygenase and/or dual inhibitors. It was therefore decided to concentrate our efforts on this site for further modifications. This resulted in the synthesis of a number of novel heterocyclic ring systems. Pharmacological test results would provide structure activity relationships for this class of lipoxygenase and/or dual inhibitors.

III. RESULTS AND DISCUSSION

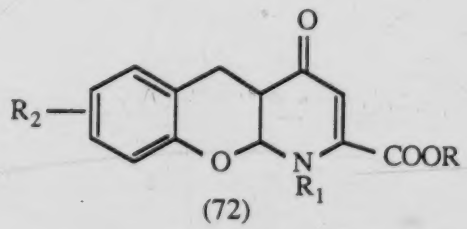
4.0. MODIFICATIONS AT THE PYRIDINE RING:

The aryl and heteroarylalkanoic acids have been one of the most widely explored groups of non-steroidal compounds for potential anti-inflammatory activity. The origin of a significant proportion of the interest in aryl and heteroarylalkanoic acid anti-inflammatory agents can be traced to pioneering work in the early 1960's by the Boots drug company in England.[130] This led to the development of a number of NSAIDs like ibuprofen and flurbiprofen etc.

The potent anti-inflammatory activity of benzopyranopyridinyl acetic acid and propionic acid derivatives has been described.[107] We were interested to see how the modification of the pyridine ring would affect the activity of the azaxanthone molecule. There was some indication from the literature that the aromatic pyridine ring might not be essential for pharmacological activity. For example, oxidation at C-4 position of the 1-azaxanthone gave the pharmacologically active 4-pyridones. Thus (71) gave 100% inhibit-



(71)

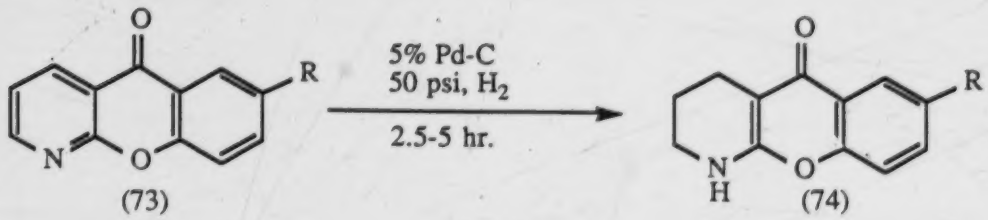


(72)

ion in the rat PCA test at 0.9 mg/kg.[131] Structurally related analogs (72), (R=H, Me; R_1=Me, Pr; R_2=H, Cl, OMe) were found to be active anti-asthmatics and anti-allergenics,[132] despite the absence of the 5-oxo substituent.

We proposed to synthesise 1,2,3,4-tetrahydrobenzopyranopyridines with various substituents and study their pharmacological properties.

4.1. Synthesis of 5H-[1]benzopyrano[2,3-b]-1,2,3,4-tetrahydropyridin-5-ones:



R	R
a) H	a) H
b) CH_3	b) CH_3
c) NH_2	c) NH_2
d) OCH_3	d) OCH_3
e) $NHCOCH_3$	e) $NHCOCH_3$
f) $CH_2COOCH_2CH_3$	f) $CH_2COOCH_2CH_3$
g) $COOCH_2CH_3$	g) $COOCH_2CH_3$
h) COOH	h) COOH
i) NO_2	
j) Br	
k) Cl	

Fig. 27: Hydrogenation of 1-azaxanthones.

The catalytic reduction of (73) was carried out in excellent yield using 5% palladium-charcoal as the hydrogenation catalyst. Reduction of (73) takes place at a pressure of 50 psi, at room temperature and a reaction time of 2.5-5 hr. (Fig. 27).

The choice of the reaction solvent did not significantly affect the product yield, and ethanol, methanol or acetic acid all gave satisfactory results. The nature of the R-substituent, whether electron-withdrawing or donating did not affect the course of the reaction at the pyridine ring. The nitro substituent of (73i), however was reduced along with the pyridine ring to give (74c). The versatility of the reduction procedure was hampered by concomitant hydrogenolysis of C-7 halogen substituents. Thus the catalytic reduction of (73j) did not give the corresponding brominated compound (74). Instead (73j)

Table 1: Yields, mp, ir and ^{1}H nmr spectral data of compounds (74 a-h)

Comp.	Yield %	mp ^{0}C[a]	ir (cm^{-1})	^{1}H nmr δ [ppm][b]
74 a	92	232	3416, 1638, 1605	1.94 (q, 2H, $CH_2\underline{CH_2}CH_2NH$, J=6.2Hz) ; 2.70 (t, 2H, $\underline{CH_2}CH_2CH_2NH$, J=6.2Hz) ; 3.46 (m, 2H, $CH_2CH_2\underline{CH_2}NH$) ; 6.56 (br, s, 1H, NH, exch.) ;7.26 (dd, 1H, 9-H, J=8.1, 1.1 Hz) 7.34 (m, 1H, 7-H) ; 7.54 (ddd, 1H, 8-H, J=8.1, 7.0, 1.6Hz) ; 8.20 (dd, 1H, 6-H, J=8.1, 1.6Hz)
74 b	93	292	3410, 1624, 1556	1.80 (q, 2H, $CH_2\underline{CH_2}CH_2NH$, J=6.3Hz) ; 2.43 (s, 3H, $\underline{CH_3}$) ; 2.66 (t, 2H, $\underline{CH_2}CH_2$-CH_2NH, J=6.3Hz) ; 3.44 (br, m, 2H, $CH_2CH_2\underline{CH_2}NH$) ; 6.84 (br, s, 1H, NH, exch.) ; 7.14 (d, 1H, 9-H, J=10.8Hz) ; 7.30 (dd, 1H, 8-H, J=10.8,3.6Hz) ; 7.94 (d, 1H, 6H, J=3.6 Hz)
74 c	93	280	3419, 3306, 1626, 1608	1.75 (q, 2H, $CH_2\underline{CH_2}CH_2NH$, J=6.25Hz) ; 2.46 (t, 2H, $\underline{CH_2}CH_2CH_2NH$, J=6.25Hz) ; 3.28 (br, m, 2H, $CH_2CH_2\underline{CH_2}NH$) ; 5.20 (s, 2H, NH_2, exch.); 6.82 (dd, 1H, 8-H, J=9.0, 2.75Hz) ; 7.05 (d, 1H, 9-H, J=9Hz) ; 7.14 (d, 1H, 6-H, J=2.8 Hz) ; 7.66 (br, t, 1H, NH, exch.)
74 d	95	235	3400, 1622, 1607	1.90 (q, 2H, $CH_2\underline{CH_2}CH_2NH$, J=6Hz) ; 2.66 (t, 2H, $\underline{CH_2}CH_2CH_2NH$, J=6Hz) ; 3.42 (m, 2H, $CH_2CH_2\underline{CH_2}NH$) ; 3.90 (s, 3H, OCH_3) ; 7.08 (dd, 1H, 8-H, J=9, 3Hz) ; 7.18 (br, s, 1H; NH, exch.) ; 7.20 (d, 1H, 9-H, J=9Hz) ; 7.57 (d, 1H, 6-H, J=3Hz)
74 e	96	315	3238, 3213, 1688 1622	1.82 (m, 2H, $CH_2\underline{CH_2}CH_2NH$) ; 2.08 (s, 3H, $COCH_3$) ; 2.54 (t, 2H, $\underline{CH_2}CH_2CH_2NH$, J=6.1Hz) ; 3.36 (br, m, 2H, $CH_2CH_2\underline{CH_2}NH$) ; 7.28 (d, 1H, 9-H, J=8.8Hz) ;

				7.80 (br, m, 1H, NH, exch.); 7.94 (dd, 1H, 8-H, J=8.8, 2.6Hz) ; 8.13 (d, 1H, 6-H, J=2.6Hz) ; 10.10 (s, 1H, $NHCOCH_3$)
74 f	90	238	3430, 1728, 1625	1.24 (t, 3H, CH_2CH_3, J=7.2Hz) ; 1.90 (m, 2H, $CH_2CH_2CH_2NH$) ; 2.67 (t, 2H, $CH_2CH_2CH_2NH$, J=6.3Hz) ; 3.43 (m, 2H, $CH_2CH_2CH_2NH$) ; 3.69 (s, 2H, CH_2CO) ; 4.15 (q, 2H, CH_2CH_3, J=7.2Hz) ; 6.40 (br, s, 1H, NH, exch.) ; 7.16 (d, 1H, 9-H, J=8.9Hz) 7.42 (dd, 1H, 8-H, J=8.9, 2.2Hz) ; 8.03 (d, 1H, 6-H, 2.2Hz)
74 g	90	238	3328, 1720, 1622	1.40 (t, 3H, CH_2CH_3, J=7.1Hz) ; 1.92 (q, 2H, $CH_2CH_2CH_2NH$, J=6.4Hz) ; 2.68 (t, 2H, $CH_2CH_2CH_2NH$, J=6.4Hz) ; 3.46 (m, 2H, $CH_2CH_2CH_2NH$) ; 4.39 (q, 2H, CH_2CH_3, J=7.1Hz) ; 6.80 (br, s, 1H, NH, exch.) ; 7.26 (d, 1H, 9-H, J=8.9Hz) ; 8.16 (dd, 1H, 8-H, J=8.9, 2.3Hz) ; 8.83 (d, 1H, 6-H, J=2.3Hz)
74 h	90	355-7	3435, 1687, 1614 br 2200-3600	1.78 (q, 2H, $CH_2CH_2CH_2NH$, J=6.2Hz) ; 2.50 (t, 2H, $CH_2CH_2CH_2NH$, J=6.2Hz) ; 3.36 (m, 2H, $CH_2CH_2CH_2NH$) ; 7.47 (d, 1H, 9-H, J=8.6Hz) ; 8.13 (dd, 1H, 8-H, J=8.6, 2.1Hz) ; 8.17 (br, s, 1H, NH exch.) ; 8.53 (d, 1H, 6-H, J=2.1Hz) ; 13.07 (br, s,1H, COOH)

(a) Compounds 74 a-d were recrystallised from ethanol ; 74e and 74g from methanol ; 74h from dioxane / methanol ; 74f from acetone

(b) Due to poor sample solubility, a solvent mixture of $CDCl_3$/DMSO-d_6 was used for compounds 74a-g ; compound 74h was dissolved in DMSO-d_6

Table 2: Mass spectral and analytical data of compounds (74 a-h)

Comp. No.	Formula	MS	Microanalyses: Found (calc.)		
		M^+ m/z(%)	C%	H%	N%
74a	$C_{12}H_{11}NO_2$	201 (32)	71.50 (71.63)	5.54 (5.51)	6.91 (6.96)
74b	$C_{13}H_{13}NO_2$	215 (84)	72.51 (72.54)	6.01 (6.09)	6.79 (6.51)
74c	$C_{12}H_{12}N_2O_2$	216 (66)	66.38 (66.65)	5.64 (5.59)	12.75 (12.95)
74d	$C_{13}H_{13}NO_3$	231 (50)	67.44 (67.52)	5.68 (5.67)	6.04 (6.06)
74e	$C_{14}H_{14}N_2O_3$	258 (1)	64.66 (65.11)	5.43 (5.46)	10.70 (10.85)
74f	$C_{16}H_{17}NO_4$	287 (100)	66.65 (66.89)	5.91 (5.96)	4.83 (4.87)
74g	$C_{15}H_{15}NO_4$	273 (100)	66.02 (65.93)	5.58 (5.53)	5.17 (5.13)
74h	$C_{13}H_{11}NO_4$	245 (100)	63.65 (63.67)	4.50 (4.52)	5.67 (5.71)

undergoes hydrogenolysis and is obtained as the hydrobromide salt of (74a) (90% yield, mp 280^{0}C from n-propanol). Basification of this salt gave a compound identical to authentic (74a). Compound (73k) behaved similarly. Compounds (74) were resistant to further reduction even with reaction times of 20 hr. The remaining double bond is tetrasubstituted and such double bonds are generally not reduced by hydrogenation. The spectral data of compounds (74a-h) are described in Table 1.

The tetrahydropyridines (74) were also obtained as byproducts in the reduction of 1-azaxanthones with sodium borohydride. The reaction was carried out in a solvent mixture of THF : isopropyl alcohol (1:1) under refluxing conditions. Monitoring of the reaction by TLC,(chloroform : methanol ; 9 :1) shows two spots for the product. The R_f value of the

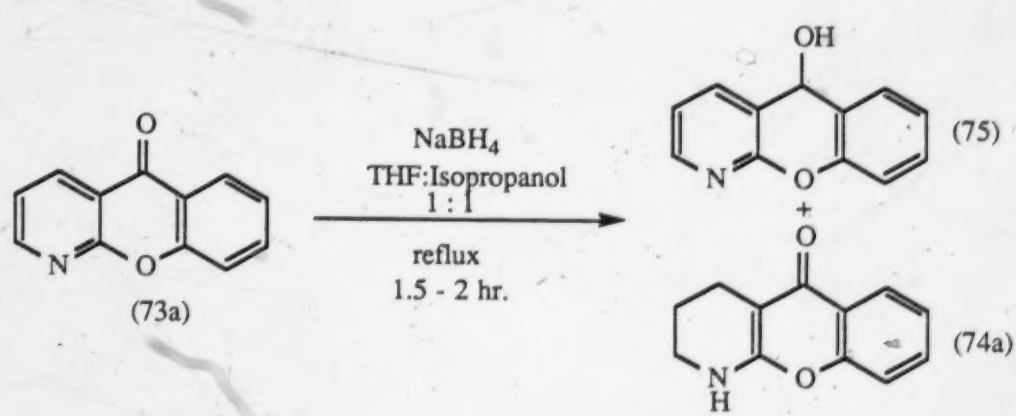


Fig. 28: Reaction of 1-azaxanthone with sodium borohydride under reflux.

lower spot was shown to be the same as that of the tetrahydropypridine (74a). The ^{1}H nmr of the reaction mixture showed that (75) and (74a) were present in a ratio of 2 : 1 approximately.

4.1.1. Synthesis of 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-carboxylic acid:

5-Oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-carboxylic acid (73h) has been obtained in low yields (37%) by the aqueous potassium permanganate oxidation of 7-

methyl-1-azaxanthone.[133] In our laboratory 1-azaxanthone-7-carboxylic acid was required in good yields for further modification to the tetrahydro derivatives (74 g,h). Therefore a sodium dichromate oxidation of 7-methyl -1-azaxanthone was explored (Fig. 29). An excellent yield (88%) of 1-azaxanthone-7-carboxylic acid (73h) was obtained by using sodium dichromate in a mixture of acetic acid and sulfuric acid (5 : 1) under reflux.

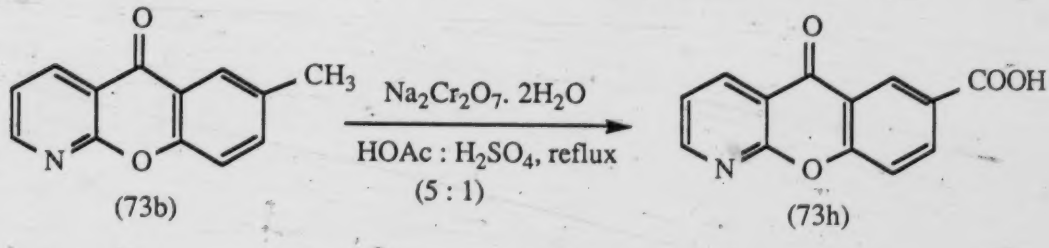


Fig. 29: Side chain oxidation of 7-methyl-1-azaxanthone.

4.1.2. Synthesis of 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid:

There are references in the patent literature for the synthesis of 1-azaxanthone-7-acetic acid (78), but a detailed synthetic procedure was not readily available.[107,134] 1-Azaxanthene-7-acetic acid has been made, starting from chloromethylation of 1-azaxanthene.[107]

In our laboratory a number of different synthetic routes were explored. Chloromethylation of 1-azaxanthone was unsuccessful , as only the starting material was obtained from the reaction mixture. Benzylic bromination of 7-methyl-1-azaxanthone with N-bromosuccinimide afforded only a 20% yield of 7-bromomethyl-1-azaxanthone. The cyclization of 2-(p-ethylacetate)phenoxynicotinic acid using polyphosphoric acid was also not successful.

7-Methyl-1-azaxanthone (73b) was converted to 1-azaxanthone-7-acetic acid (78) in 53% yield by a synthetic scheme shown in Fig.30. Benzylic bromination with bromine

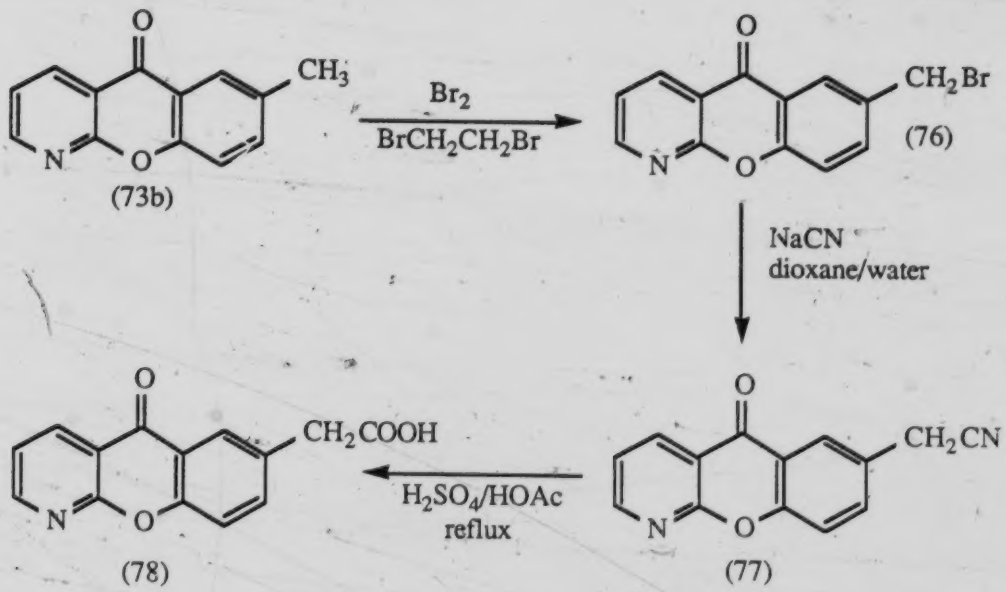


Fig. 30: Synthesis of 1-azaxanthone-7-acetic acid.

in 1,2-dibromoethane gave the benzyl bromide derivative (76). The crude (76) was reacted with sodium cyanide to give the 1-azaxanthone-7-acetonitrile (77). Acid hydrolysis of the nitrile (77) provided 1-azaxanthone-7-acetic acid (78). Compound (78) is easily converted to its ethyl ester by refluxing in 98% ethanol, containing a trace amount of sulfuric acid.

4.2. Synthesis of 3-(2-hydroxybenzoyl)-1-methyl-2(1H)-pyridinones:

Methyl iodide salts of 1-azaxanthones were synthesized to explore the reactivity of the pyridine ring, by reduction to 1,2-dihydropyridines and oxidation to 2-pyridinone derivatives.[135] Further studies on the reactivity of methyl iodide salts of 1-azaxanthones led to the synthesis of 3-benzoyl-1-methyl-2-pyridinones (80).

Anti-inflammatory 2-pyridinones have been reported in the literature.[136,137] Isonixin (2,6-dimethylanilide of 2-pyridinone-3-carboxylic acid) has been marketed as a non-ulcerogenic anti-inflammatory, analgesic agent.[138] 2-Pyridinones (80) are an attractive synthetic target as they contain a carboxylic acid function, also present in many NSAIDs. The phenolic function is desirable since it may play a role in scavenging hydroxy radicals

believed to be mediators in the inflammatory process.[139] In addition, o-acetylation would provide derivatives potentially capable of transacylating the cyclooxygenase enzyme. It is believed that aspirin acts by acylating the cyclooxygenase enzyme.[69]

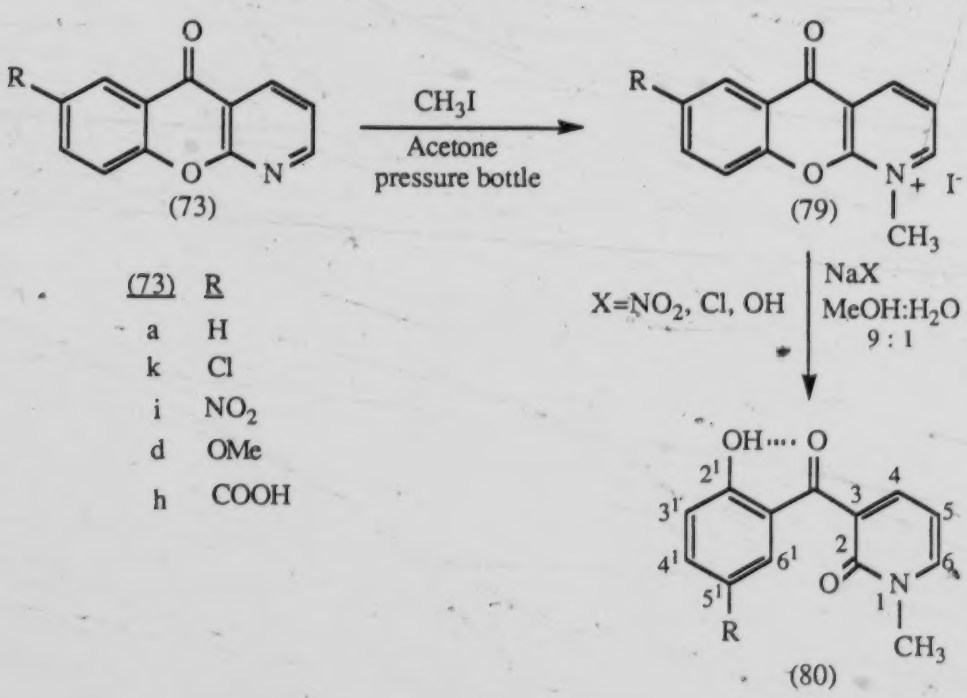


Fig. 31: Synthesis of 3-(2-hydroxybenzoyl)-1-methyl-2(1H)-pyridinones.

N-Methylation of benzopyranopyridines (73) with iodomethane was conducted in a glass pressure bottle. Acetone was the solvent of choice since compounds (73) are soluble on heating.The methyl iodide salts (79) precipitate from solution in high yields as bright yellow crystals. Compounds (79) were then stirred with refluxing, for 0.5-1.5 hr. in methanol / water (9 : 1 v/v) containing one equivalent of sodium nitrite. Yields of (80) were between 68-95% (Fig. 31). Sodium chloride rather than nitrite is also effective in promoting ring opening. When sodium hydroxide was used, in some cases a mixture of

Table 3: 3-(2-Hydroxybenzoyl)-1-methyl-2(1H)-pyridinones (80 a-k)[a]

Comp.	Yield%	mp^{0}C (MeOH)	ir (KBr) ν (cm^{-1})	^{1}H nmr δ (ppm)
80 a	95	127-128	1665, 1660, 1640	3.64 (s, 3H, NCH_3) ; 6.34 (t, 1H, 5-H, J=6.76Hz) ; 6.90 (m, 1H, 5^1-H) ; 7.05 (dd, 1H, 3^{1}H, J=1,06Hz) ; 7.58 (m, 4H, 4-H, 4^1-H, 6-H, 6^1-H) ; 11.92 (s, 1H, OH, exch.)
80 k	91	179	1665, 1660, 1638	3.65 (s, 3H, NCH_3) ; 6.35 (t, 1H, 5-H, J=7Hz) ; 7.02 (d, 1H, 3^1-H, J=9Hz) 7.46 (dd, 1H, 4^1-H, J=9, 2.5Hz) ; 7.52 (d, 1H, 6^1-H, J=2.5Hz) ; 7.61 (m, 2H, 4-H, 6-H) ; 12.04 (s, 1H, OH, exch.)
80 i	92	220	1671, 1647, 1548 1335	3.66 (s, 3H, NCH_3) ; 6.47 (t, 1H, 5-H, J=6.82) ; 7.15 (d, 1H, 3^1-H, J=8.68Hz) 7.88 (m, 2H, 4-H, 6-H) ; 8.34 (dd, 1H, 4^1-H, J=8.68, 2.80 Hz) ; 8.48 (d, 1H, 6^1-H, J=2.8Hz) ; 12.20 (br, s, 1H, OH, exch.)
80 d	93	131-132	1690, 1660, 1635	3.66 (s, 3H, NCH_3) ; 3.76 (s, 3H, OCH_3) ; 6.35 (t, 1H, 5-H, J=6.83Hz) 7.00 (d, 1H, 3^1-H, J=9.34Hz) ; 7.03 (d, 1H, 6^1-H, J=2.87Hz) ; 7.18 (dd, 1H, 4^1-H, J=9.34, 2.87Hz) ; 7.60 (m, 2H, 4-H, 6-H) ; 11.60 (s, 1H, OH, exch.)

80 h	68	243	br, 3500-2300	3.62 (s, 3H, NCH_3) ; 6.4 (t, 1H, 5-H, J=6.8Hz) ; 7.06 (d, 1H, 3^1-H, J=8.5Hz) 7.74 (dd, 1H, 6-H, J=7.12, 2.24Hz) ; 7.90(dd, 1H, 4-H, J=6.73, 2.16Hz) ; 8.12 (dd, 1H, 4^1-H, J=8.36, 1.85Hz) ; 8.22 (d, 1H, 6^1-H, J=2.16Hz) ; 13.5 (s, 1H, OH or COOH, exch.)

a) The microanalyses were within ± 0.4% of the calculated values.

pyridinone (80) and a tricyclic 5-oxo-2-pyridinone was formed.[140]

The probable mechanism of the reaction can be illustrated as shown in (Fig. 32). Confirmation of the structure (80) was based on spectral data. A common feature of most 3-substituted -2-pyridinones is the presence of a triplet (J=6.8Hz) at approximately 6.4 δ in the proton nmr spectrum. This signal is assigned to the 5-H pyridinone proton and arises due to equivalent coupling with the 4-H and 6-H protons. In addition, the phenolic proton appears at 11.5-12.0 δ indicating significant intramolecular hydrogen bonding with the ketone group. Such pyridinones (80) were previously obtained from the reaction of 1-azaxanthone with excess potassium hydroxide in ethanol.[126] The spectral data of compounds (80-a-k) are described in Table 3.

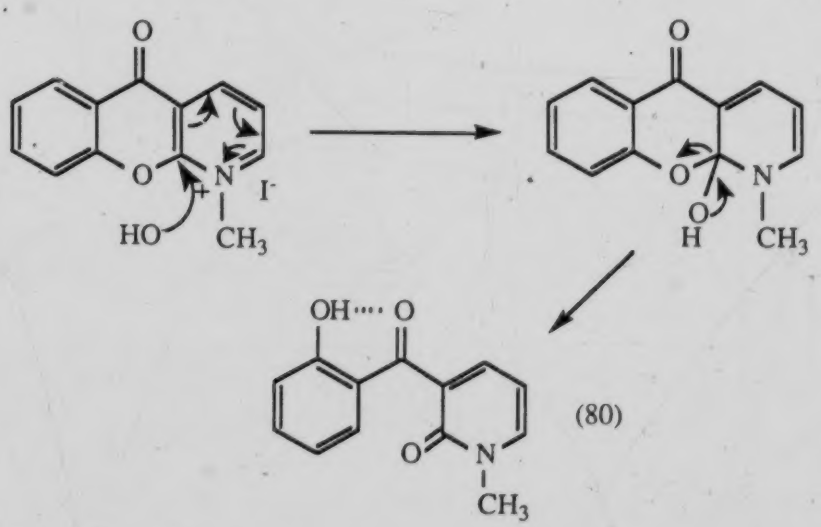


Fig. 32: Probable mechanism of ring opening of methyl iodide salt of 1-azaxanthone.

5.0. MODIFICATIONS AT THE C-5 POSITION:

5.1. Synthesis of 5H-[1]benzopyrano[2,3-b]pyridine:

Conversion of 1-azaxanthone to 1-azaxanthene is an important reaction since it alters the chemical reactivity of the molecule as well as its pharmacological properties. It has been shown that the reduction of a C-5 carbonyl function to the methylene group enhances the anti-inflammatory activity in a series of benzopyranopyridinylacetic acid and propionic acid derivatives.[107] The most active compound in that series pranoprofen (7) is a 7-propionic acid derivative of 1-azaxanthene. Other 1-azaxanthene derivatives (72) have been shown to be active anti-asthmatics and anti-allergenics.[132]

Conventional procedures to reduce a ketone functional group to methylene, like Wolff-Kishner and Clemmensen reduction, were unsuccessful. A two step sodium borohydride reduction of 1-azaxanthone gave 1-azaxanthene in about 80% yield. 1-Azaxanthone was first reduced to 1-azaxanthen-5-ol using sodium borohydride and methanol as the solvent. The alcohol (75) was then dissolved in a small quantity of trifluoroacetic acid and reduced further to (81) by slow and careful addition of sodium borohydride (Fig. 33).[141]

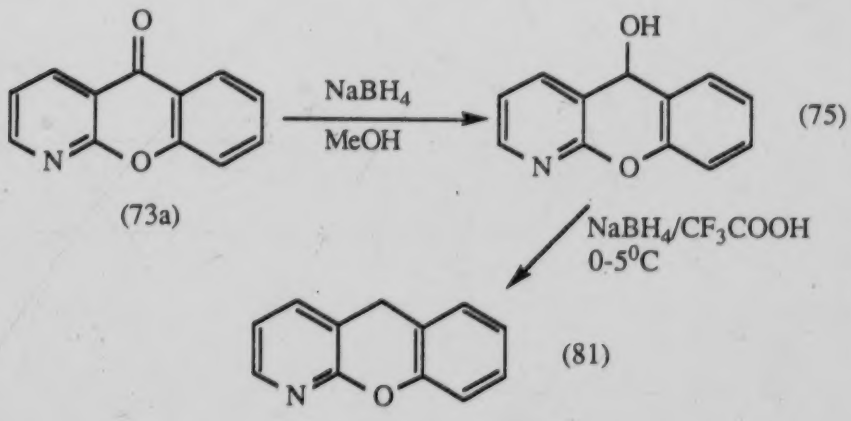
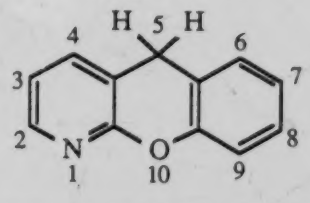


Fig. 33: Synthesis of 1-azaxanthene.

It was also found that the reduction of the alcohol (75) to 1-azaxanthene (81) could be accomplished using glacial acetic acid instead of trifluoroacetic acid. It is likely that the conversion of (75) to (81) involves the formation of a stabilised carbo-cation in trifluoroacetic acid or glacial acetic acid and then quenching of the carbo-cation by a hydride species.[142]

The 300 MHz ^1H nmr spectrum (δ) of azaxanthene (81) exhibited a characteristic 2H singlet at 4.12 due to the C-5 methylene protons. The 5H multiplet at 7.04-7.32 was assigned to C-3,6,7,8 and 9 hydrogens. The two multiplets at 7.58 and 8.24 were assigned to C_4-H and C_2-H hydrogens, respectively. We expected the absorptions of C_2-H and C_4-H to be doublet of doublets. A 6.78 Hz/cm expansion of the spectrum clearly shows the C_2-H and C_4-H signals to be multiplets. A likely explanation is long range coupling to the C-5 methylene hydrogens which was confirmed by a decoupling experiment. Irradiation of the C-5 methylene singlet at 4.12 simplifies both the C_2-H and C_4-H into the expected doublet of doublets.



(81)

5H-[1]benzopyrano[2,3-b]pyridine (1-azaxanthene)

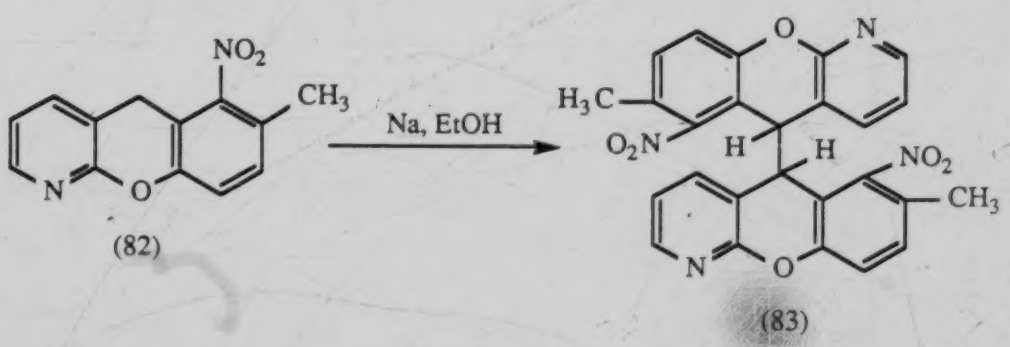
Similar long range couplings have been observed in a number of fluorene and azafluorene derivatives.[142] The magnitude of these long range coupling constants were measured by five and six spin calculations. They were shown to be between 0.3-0.9 Hz.

Hydrogenation of 1-azaxanthen-5-ol (75) in the presence of 10% palladium-charcoal as the catalyst and 40 psi pressure also afforded 1-azaxanthene in low yields (35-50%). A Raney nickel desulfurization of 5(ethylthio)-5H-[1]benzopyrano[2,3-b]pyridine

(prepared by refluxing 1-azaxanthene-5-ol and ethane thiol under acidic conditions) gave a 50% yield of 1-azaxanthene (81).

5.2. Synthesis of 6,6'-dinitro-7,7'-dimethyl-5,5'-bi-1-azaxanthen (dimer) :

7-Methyl-6-nitro-1-azaxanthene (prepared by nitration of 7-methyl-1-azaxanthone and two step sodium borohydride reduction) when treated with sodium in ethanol afforded the dimer (83) in good yield (77%).



(82) (83)

Fig. 34: Synthesis of 1-azaxanthene dimer (83).

Similar dimers in the xanthene series are known. They have been prepared by the oxidation of xanthene (e.g. by benzoquinone) in sun light or by the reduction of xanthione using zinc and hydrochloric acid.[143]

A radical intermediate is probably involved in the formation of the dimer (83) (Fig.35). The stability of the radical is enhanced by resonance with the adjacent nitro group.

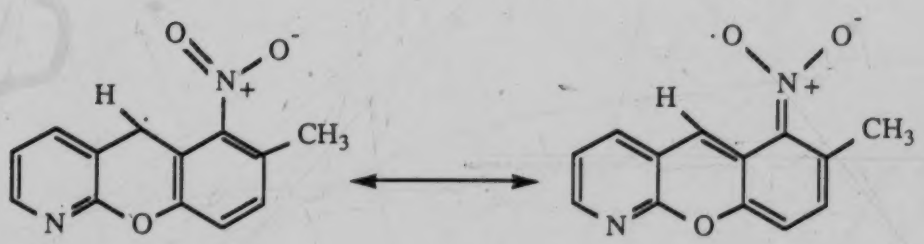


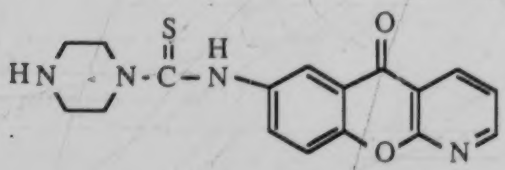
Fig. 35: Resonance stabilization of the radical intermediate.

Azaxanthene dimer was also obtained as byproduct in the attempted Raney nickel desulfurization of 5-[ethylthio]-5H-[1]benzopyrano[2,3-b]pyridine to give 1-azaxanthene. The Raney nickel desulfurization reaction is known to involve radical intermediates.[144]

The ^1H nmr spectra (δ) of dimer (83) displayed a 3H singlet at 2.42 due to the 7-methyl group. The C_5-H proton appears as a singlet at 4.58. The doublet of doublets at 6.6 (J=7.46, 1.93 Hz) is due to C_4-H. This high field absorption of 4-pyridine hydrogen may be due to the diamagnetic anisotropic shielding effect caused by the 6'-nitro group. The C_3-H is displayed as a doublet of doublet (J=7.46, 4.98 Hz) at 6.82. Two doublets at 7.02 and 7.3 were assigned to C_9-H and C_8-H, respectively. The doublet of doublet at 8.24 (J=4.97, 1.93 Hz) was assigned to C_2-H. The ir spectrum (cm^{-1}) displayed absorptions at 1532 and 1433 (NO_2), while the chemical ionization mass spectrum (NH_3) exhibited (m+1) = 483. The microanalytical results were within (±0.4%) of calculated values. These results are consistent with the structure of the dimer (83).

6.0. MODIFICATIONS AT THE BENZENE RING:

The preliminary pharmacological screening of compounds prepared by other investigators in our laboratory revealed that nitrogen containing substituents in general at the C-7 position of 1-azaxanthone gave compounds (e.g. 84, 85) which were lipoxygenase inhibitors.



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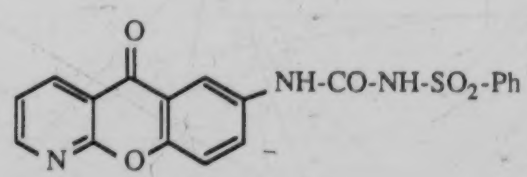
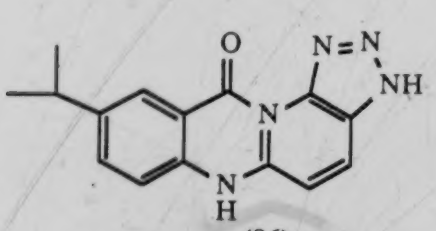


(85)

Continuation of this work led to the development of compounds with fused five membered nitrogen containing aromatic rings at the C-6,7 or C-7,8 positions of 1-

azaxanthone or 1-azaxanthene (e.g. 90, 94, 105). These compounds were generally more potent than the simple C-7 substituted azaxanthone derivatives.

Based on these preliminary pharmacological results, it was evident that compounds with nitrogen containing heterocyclic rings fused across C-6,7 or C-7,8 of 1-azaxanthone or 1-azaxanthene were attractive pharmacological leads. Further support was evident in the literature where several fused tetracyclic compounds had been reported. Quinazoline derivatives (86) and (87) are orally active anti-allergic agents against PCA in rats (ED_{50} = 0.25mg/kg).[145]



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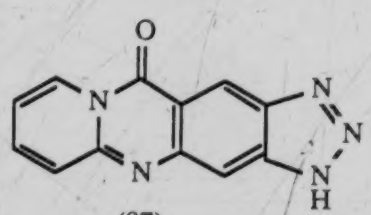


(87)

6.1. FIVE MEMBERED RING WITH 2 NITROGENS:

6.1.1.Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e]benzimidazol-11(1H,11H)-one:

7-Amino-1-azaxanthone (73c) has been prepared from 7-nitro-1-azaxanthone by various methods in our laboratory. Reduction with ferrous sulphate-ammonia, stannous chloride in concentrated HCl or 10% palladium-charcoal and hydrazine all gave (73c) in good yields. Surprisingly the reported synthesis[108] of (73c) involved hydrogenation of 7-nitro-1-azaxanthone over palladium-charcoal at 60 psi whereas in our own hands similar conditions gave 7-amino-5H-[1]benzopyrano[2,3-b]1,2,3,4-tetrahydropyridin-5-one (74c) as the exclusive product. N-Acetylation with acetic anhydride in acetic acid gave 7-acetamido-1-azaxanthone (73e) in 88% yield. Compound (73e) was nitrated under standard

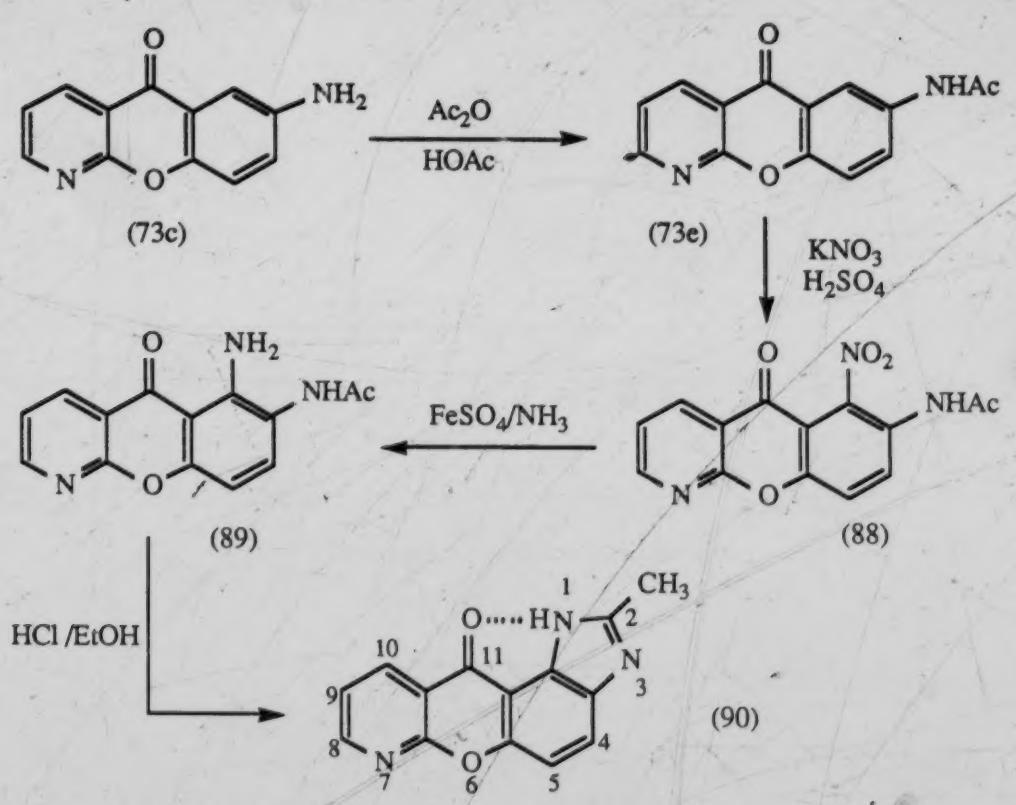


Fig. 36: 2-Methylpyrido[3',2':5,6]pyrano[3,2-e]benzimidazol-11(1H,11H)-one.

conditions (KNO_3 / H_2SO_4) to give (88) in 64% yield. Although the C-5 carbonyl is expected to deactivate the C-6 position, nitration occurs solely at this position. The position of the nitro substituent in (88) was unequivocally established by ^1H nmr. Substitution at C-9 would give rise to doublets (meta-coupling) for C-6 and C-8 protons. Substitution at C-8 would also give doublets, but with para-coupling, or singlets if para-coupling was very small. The ^1H nmr of (88) shows doublets (J=8.97 Hz) at δ 7.95 and 8.17 for the C-9 and C-8 protons, respectively. The magnitude of the coupling constant indicates that the protons are ortho to each other. Reduction of (88) with ferrous sulfate, ammonia affords (89) which undergoes cyclization under acidic conditions to give the title compound (90) in 65% yield (Fig. 36). It was found that the cyclization also occurs by refluxing a methanolic solution of (89) in the presence of sodium hydroxide.

The structure of (90) was confirmed by means of spectral and micro-analytical data. The 300 MHz ^{1}H nmr spectra (δ) of (90) shows a 3H singlet at 2.62 due to the 2-methyl group. Two doublets at 7.5 and 8.09 (J= 8.73 Hz) were assigned to C-5 and C-4 protons, respectively. The absorption of the C-5 proton is upfield compared to C-4, due to the resonance effect of the oxygen unshared electrons.This assignment is also based on comparison with the δ values of C_8-H and C_9-H in C-7 substituted 1-azaxanthones. Three doublet of doublets at 7.67 (J=7.78, 4.55 Hz), 8.75 (J=7.78, 2.09 Hz) and 8.89 (J=4.55, 2.09 Hz) were readily assigned to C-9, C-10 and C-8 protons, respectively, based on their J values.The 1-NH proton appeared as a singlet at 12.99 and was exchangeable with D_2O. This down field absorption of the NH proton may be due to hydrogen bonding with the carbonyl oxygen (Fig. 36).The ir spectrum (cm^{-1}) showed peaks at 3435 and 1652 attributed to N-H and C=O, respectively. The high resolution mass spectrum shows a base peak corresponding to the molecular ion (exact mass calculated for $C_{14}H_9N_3O_2$: 251.0695 ; found : 251.0688).

6.1.2. Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e](1H,11H)benzimidazole :

7-Acetamido-6-nitro-1-azaxanthone (88) was reduced to 7-acetamido-6-nitro-1-azaxanthen-5-ol (91) with sodium borohydride in methanol. The alcohol (91) was dissolved in trifluoroacetic acid and further reduced to 7-acetamido-6-nitro-1-azaxanthene (92) with sodium borohydride. Reduction of (92) with palladium-charcoal and hydrazine affords the azaxanthene (93), which was cyclized to the benzimidazole (94), by refluxing in a mixture of hydrochloric acid : ethanol (2 :1) (Fig. 37).

The 300 MHz ^{1}H nmr spectrum (δ) of (94) shows two singlets at 2.55 and 4.34. The 3H singlet at 2.55 was assigned to the 2-methyl group and the 2H singlet at 4.34 was assigned to the C-11 methylene protons. The two doublets at 6.94 and 7.32 (J=8.56 Hz) are attributed to C_5-H and C_4-H respectively. The doublet of doublets at 7.14 (J=7.3, 4.66 Hz) was attributed to C_9-H.Two doublets at 7.78 (br, J=7.3 Hz) and 8.15 (br, J=4.66 Hz)

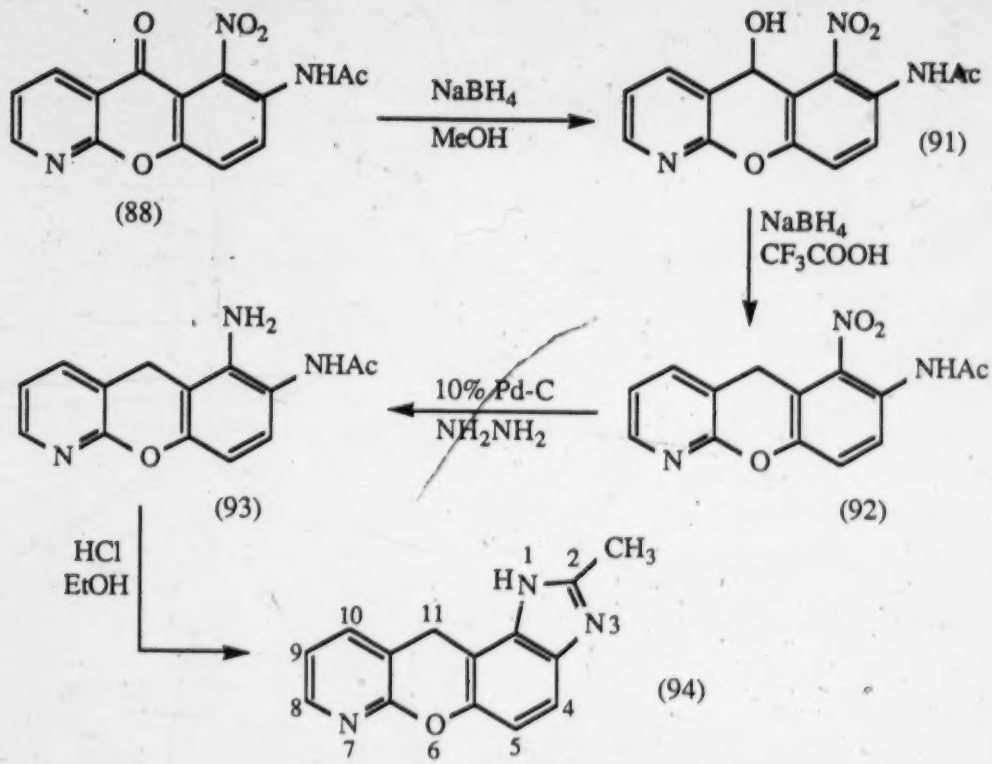


Fig. 37:Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e](1H,11H)benzimidazole.

were easily assigned to C_{10}-H and C_8-H respectively, based on their chemical shifts and J values. The ir spectrum (cm^{-1}) exhibited absorptions at 3418 (NH) and 1630 (C=N), while the high resolution mass spectrum displayed a molecular ion corresponding to $C_{14}H_{11}N_3O$: Mass calculated, 237.0901 ; mass found, 237.0889.

6.1.3. Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzimidazole :

7-Acetamido-1-azaxanthone (73e) was reduced to 7-acetamido-1-azaxanthene (95) in two steps using sodium borohydride in methanol and sodium borohydride in acetic acid respectively. Nitration of (95) under standard conditions afforded 7-acetamido-8-nitro-1-azaxanthene (96). The position of the nitro group was confirmed by the ^1H nmr spectrum

of (96). It showed two singlets at δ 7.54 and 7.76 for the C-6 and C-9 protons, respectively. These protons therefore have a para-relationship with a coupling constant <1.

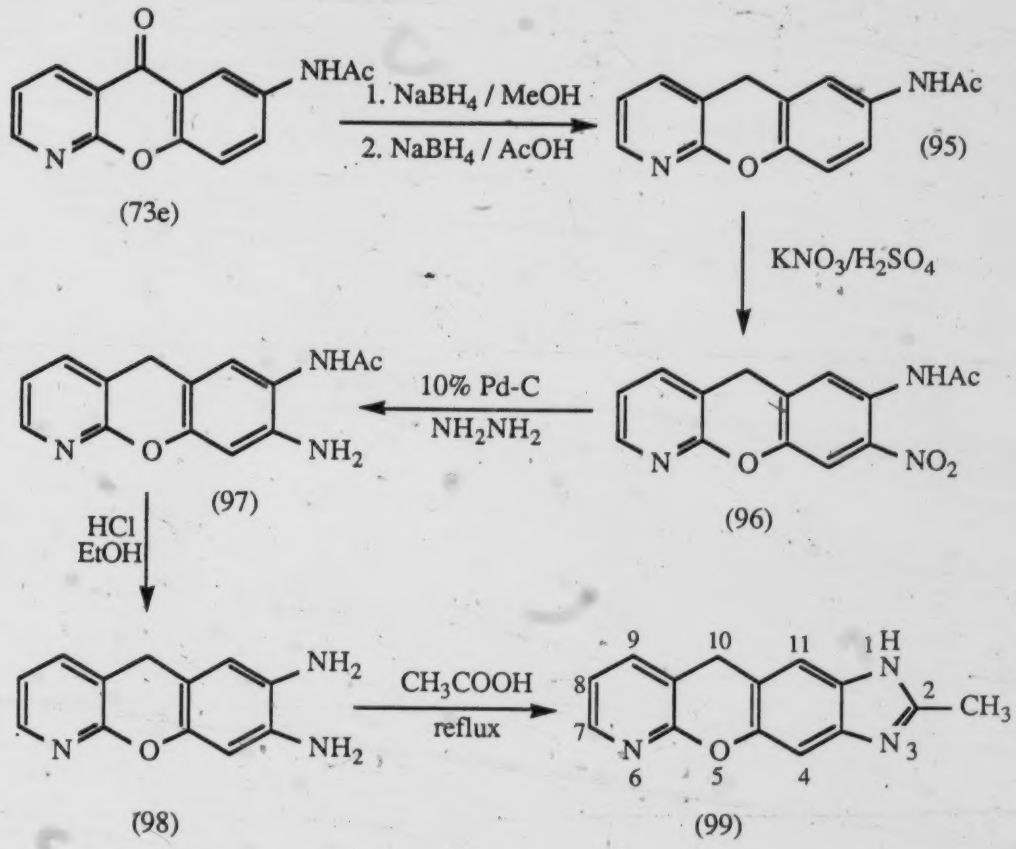


Fig. 38: Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzimidazole.

If nitration occurred at C-6, the spectrum would show two doublets (ortho coupling) for the C-8 and C-9 protons. It is interesting to note that in the absence of the C-5 carbonyl, electrophilic aromatic substitution takes place at the C-8 rather than C-6 position. This implies that in the latter instance the carbonyl group may have a directing effect on the incoming electrophile, resulting in the exclusive formation of a C-6 substituted product (section 6.1.1). 7-Acetamido-8-nitro-1-azaxanthene (96) was reduced to 7-acetamido-8-amino-1-azaxanthene (97) by refluxing in ethanol with 10% palladium-charcoal and

hydrazine. The attempted direct cyclization of (97) using hydrochloric acid : ethanol (2:1), resulted in the formation of the diamino compound (98), with a small quantity of the cyclized product (99). The diamino compound was cyclized to the benzimidazole (99) in good yields (78%), by refluxing in glacial acetic acid (Fig. 38).

The ^{1}H nmr spectrum (δ) of (99) showed two singlets at 2.46 (3H) and 4.2 (2H) attributed to the 2-methyl and 10-methylene hydrogens respectively. The singlets at 7.24 and 7.38 were assigned to C_4-H and C_{11}-H, respectively. The C_8-H absorption appeared as a doublet of doublets (J=7.34, 4.33 Hz) at 7.16, while the C_9-H and C_7-H absorptions appeared as broad doublets at 7.76 (J=7.34 Hz) and 8.18 (J=4.33 Hz) respectively. The ir (cm^{-1}) spectrum exhibited absorptions at 3133 (N-H), 2918 (C-H) and 1581 (C=C) while the high resolution mass spectrum displayed a molecular ion corresponding to $C_{14}H_{11}N_3O$: Mass calculated, 237.0901; mass found, 237.0895.

6.2. FIVE MEMBERED RING WITH 3 NITROGENS:

The pharmacological evaluation of benzimidazoles (e.g. 90, 94, 99) suggested that nitrogen containing five membered rings at C-6,7 and C-7,8 positions of 1-azaxanthone are an important structural feature for lipoxygenase inhibiting activity. This inference was also supported by tetracyclic compounds (e.g. 86, 87) reported in the literature.[145] Therefore it was proposed to further extend the series and synthesize compounds incorporating triazole, thiazole and pyrrole rings (e.g. 100, 105, 108)

6.2.1. Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]benzotriazol-11(1H,11H)-one:

Diazotization[146] of 7-acetamido-6-amino-1-azaxanthone (89) using a mixture of concentrated hydrochloric acid and sodium nitrite afforded the benzotriazole (100) in high yield (85%). The acetyl group was also hydrolysed during the reaction (Fig. 39).

The structure of (100) was confirmed by spectral and and microanalytical data. The 300 MHz ^{1}H nmr spectrum (δ) of benzotriazole (100) displayed a 2H multiplet at 7.76 due

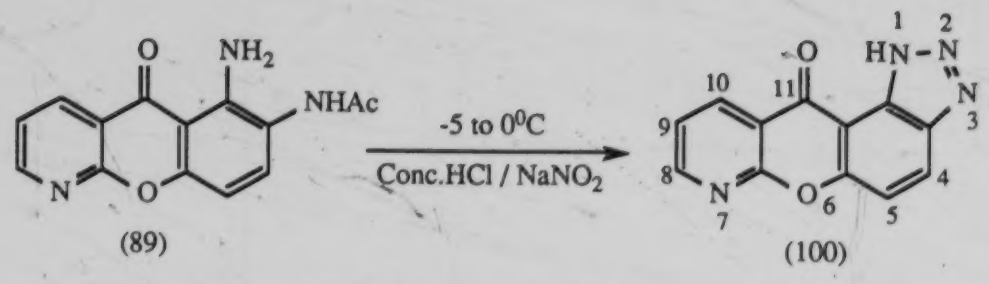


Fig. 39: Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]benzotriazole-11(1H,11H)-one.

to C_5-H and C_9-H. The doublet at 8.62 (J=10.02 Hz) is attributed to C_4-H. Two doublet of doublets at 8.8 (J=7.51, 1.78 Hz) and 8.94 (J=4.51, 1.78 Hz) are assigned to C_{10}-H and C_8-H respectively. The singlet at 9.9 was broad and exchangeable with D_2O. It was assigned to the N-H proton. The ir spectrum (cm^{-1}) of benzotriazole (100) exhibited absorptions at 3500 (N-H) and 1635 (C=O). The microanalytical data was within (±0.4%) of calculated values.

The synthetic methods for benzotriazoles described in the literature[146,147] use 1,2-diamino compounds as precursors for diazotization. Diamino compounds like (98) are frequently difficult to purify and handle. The procedure described above makes use of the acetamido-amino compound (89) which is easier to prepare and handle.

6.2.2. Synthesis of pyrido[3',2':5,6]pyrano[3,2-e](1H,11H)benzotriazole:

Benzotriazole (101) was prepared by the diazotization of 7-acetamido-6-amino-1-azaxanthene (93), (Fig.40). The synthesis of azaxanthene (93) is described in Fig. 37. The structure of the benzotriazole (101) was established from spectral data. The 300 MHz ^1H nmr spectrum (δ) of (101) exhibits a 2H singlet at 4.46 due to the C-11 methylene group. The 2H multiplet at 7.26 was assigned to C_5-H and C_9-H. At 7.84 is a doublet (J=8.84 Hz) due to C_4-H. Two doublet of doublets at 7.90 (J=7.32, 2.20 Hz) and 8.22 (J=4.72, 2.20 Hz) were attributed to C_{10}-H and C_8-H, respectively. The ir spectrum (cm^{-1}) showed absorptions at 3405 (N-H) and 1580 (C=C). The high resolution mass spectrum exhibited

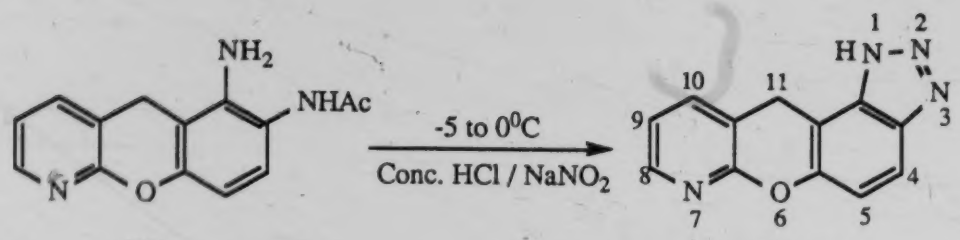


Fig. 40: Synthesis of pyrido[3',2':5,6]pyrano[3,2-e](1H,11H)benzotriazole.

a molecular ion corresponding to $C_{14}H_{11}N_3O$: Mass calculated, 224.0698 ; mass found, 224.0694.

6.2.3. Synthesis of pyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzotriazole :

Diazotization of 7-acetamido-8-amino-1-azaxanthene (97) affords the benzotriazole (102) in good yield (73%) (Fig. 41).

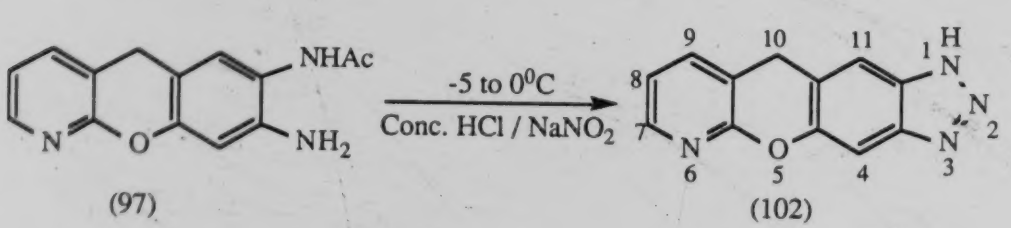


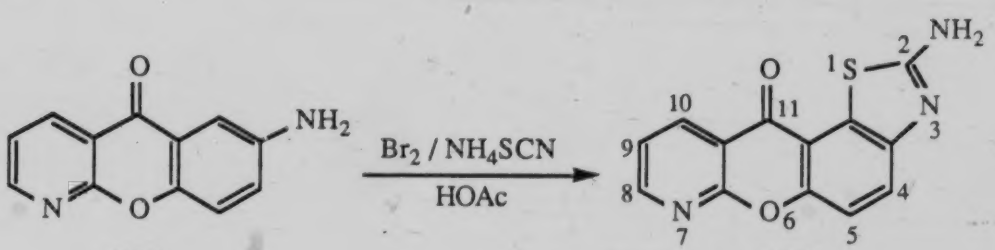
Fig. 41: Synthesis of pyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzotriazole.

The 300 MHz ^1H nmr spectrum (δ) of benzotriazole (102) exhibited a 2H singlet at 4.32 due to the C-10 methylene protons. The two doublet of doublets at 7.22 (J=7.25, 4.06 Hz) and 7.84 (J=7.25, 2.32 Hz) are due to C_8-H and C_9-H, respectively, while C_4-H and C_{11}-H appear as singlets at 7.66 and 7.92. The broad doublet at 8.2 (J=4.0 Hz) was assigned to C_7-H. The ir spectrum (cm^{-1}) showed absorption at 3460 (N-H). The high resolution mass spectrum displayed a molecular ion corresponding to $C_{14}H_{11}N_3O$: mass calculated, 224.0698 ; mass found, 224.0702.

6.3. FIVE MEMBERED RING WITH 1 NITROGEN AND 1 SULFUR:

6.3.1. Synthesis of 2-aminopyrido[3',2':5,6]pyrano[2,3-g]benzothiazol-11(11H)-one:

The preparation of (73c) has already been described under section (6.1.1). Treatment of 7-amino-1-azaxanthone (73c) with ammonium thiocyanate and bromine[148] gave a good yield of the benzothiazole (103), (Fig. 42). It precipitated as a hydrobromide salt, which was filtered and basified with sodium carbonate solution, to generate the free amine.



(73c) (103)

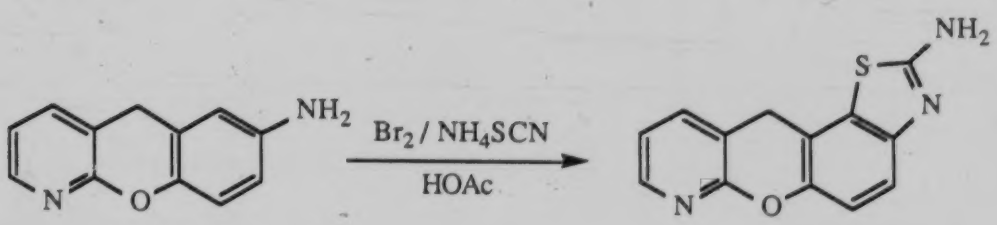
Fig. 42: Synthesis of 2-aminopyrido[3',2':5,6]pyrano[2,3-g]benzothiazol-11(11H)-one.

The mixture of bromine and thiocyanate[149] produces the reactive thiocyanogen $(SCN)_2$. 7-Amino-1-azaxanthone reacts readily with thiocyanogen at C-6, to form 7-amino-6-thiocyanate-1-azaxanthone *in situ* , which then cyclizes immediately to the benzothiazole (103). Formation of the thiazole ring across the C-6, C-7 positions of the 1-azaxanthone molecule (103) could be easily confirmed by the ^1H nmr spectrum. The spectrum exhibited an ortho coupled doublet (J=8.94 Hz) at δ 7.92 for the C_4-H. The other ortho coupled doublet for C_5-H was merged with absorptions for C_9-H and C-2 amino protons to appear as a multiplet at δ 7.68. If the ring formation had occurred between the C-7 and C-8 positions of the azaxanthone molecule, there would be two singlets for the two remaining protons on the benzene ring. The other absorptions seen in the spectrum were two broad doublets at δ 8.68 (J=7.56 Hz) and 8.84 (J=3.44 Hz), assigned to C_{10}-H and C_8-H, respectively. The ir spectrum (cm^{-1}) showed absorptions at 3443, 3304 (NH_2)

and 1646 (C=O). The microanalytical data supported the molecular formula of (103) corresponding to $C_{13}H_7N_3O_2S$.

6.3.2. Synthesis of 2-aminopyrido[3',2':5,6]pyrano[2,3-g](11H)benzothiazole :

7-Amino-1-azaxanthene (104) was prepared by the acid hydrolysis of 7-acetamido-1-azaxanthene (95). Reaction of azaxanthene (104) with thiocyanogen, afforded benzothiazole (105) (Fig.43). It is interesting to note that the substitution of thiocyanate (SCN), takes place at the C-6 position of azaxanthene. This is in contrast to the nitration of 7-acetamido-1-azaxanthene, which takes place at the C-8 position (section 6.1.3.)



(104) (105)

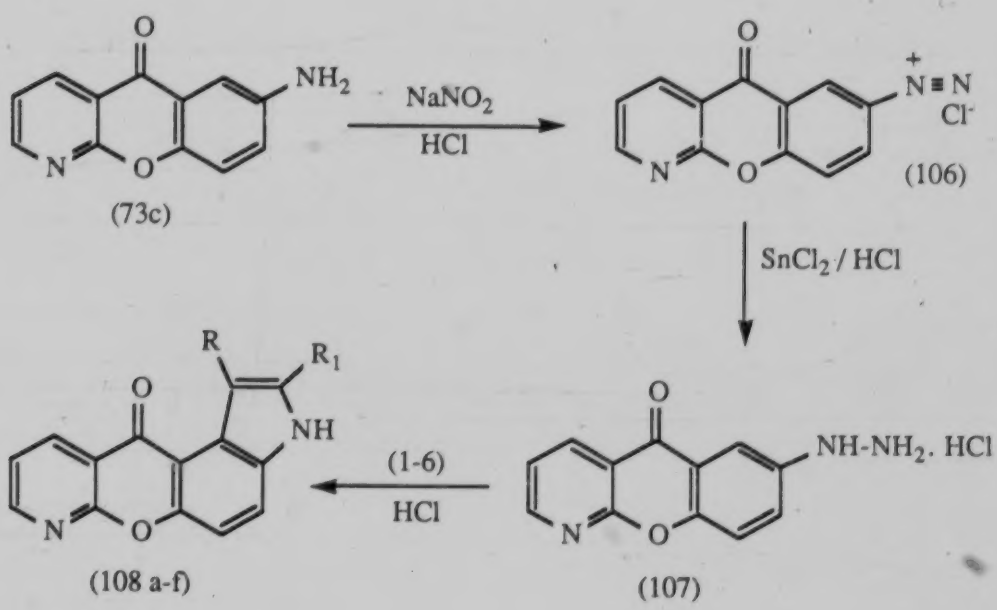
Fig. 43: Synthesis of 2-aminopyrido[3',2':5,6]pyrano[2,3-g](11H)benzothiazole.

The ^1H nmr spectrum (δ) of the benzothiazole (105) displayed a 2H singlet at 4.16, assigned to C-11 methylene hydrogens.Two doublets at 7.08 and 7.30 (J=8.44 Hz) were attributed to C_5-H and C_4-H respectively. The doublet of doublet at 7.22 (J=7.19, 4.21 Hz) was due to C_9-H. Two broad doublets at 7.86 (J=7.19 Hz) and 8.22 (J=4.21 Hz) were due to C_{10}-H and C_8-H, respectively. The ir spectrum (cm^{-1}) displayed absorptions at 3287, 3123 (NH_2) and 1638 (C=N) while the high resolution mass spectrum exhibited a molecular ion corresponding to $C_{13}H_9N_3SO$: Mass calculated, 255.0466; mass found, 255.0452.

6.4. FIVE MEMBERED RING WITH 1 NITROGEN:

6.4.1. Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]indol-11(3H,11H)-ones:

Diazotization of 7-amino-1-azaxanthone (73c) with sodum nitrite and concentrated hydrochloric acid afforded the diazonium chloride (106), which was further reduced to 7-hydrazino-1-azaxanthone (107) with stannous chloride. Reaction of (107) with carbonyl compounds (1-6), under acidic conditions gave good yields of the title compounds (108 a-f) (Fig. 44).



(108 a) R=CH_3, R_1=H
(108 b) R=C_4H_9, R_1=CH_3
(108 c) R=C_5H_{11}, R_1=CH_3
(108 d) R=Ph, R_1=H
(108 e) R, R_1=CH_2-CH_2-CH_2-CH_2
(108 f) R, R_1=CH_2-CH_2-CH_2

(1) Propionaldehyde
(2) 2-Heptanone
(3) 2-Octanone
(4) Phenyl acetaldehyde
(5) Cyclohexanone
(6) Cyclopentanone

Fig. 44: Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]indol-11(3H,11H)-ones.

Of the alternatives available for the preparation of the indole ring system, the Fischer indole route[150] was chosen because of its versatility. The procedure used was reported by M.A.Khan and Morley[151] The phenyl hydrazone of an aldehyde or ketone is heated in the presence of a catalyst such as zinc chloride, boron trifluoride, polyphosphoric acid or hydrochloric acid, to produce an indole.

The Fischer synthesis involves rearrangement with the loss of a molecule of ammonia. The mechanism by which such a molecular manipulation occurs has been the object of several studies.[152,153] The scheme which most satisfactorily explains the various known aspects is shown in Fig. 45.

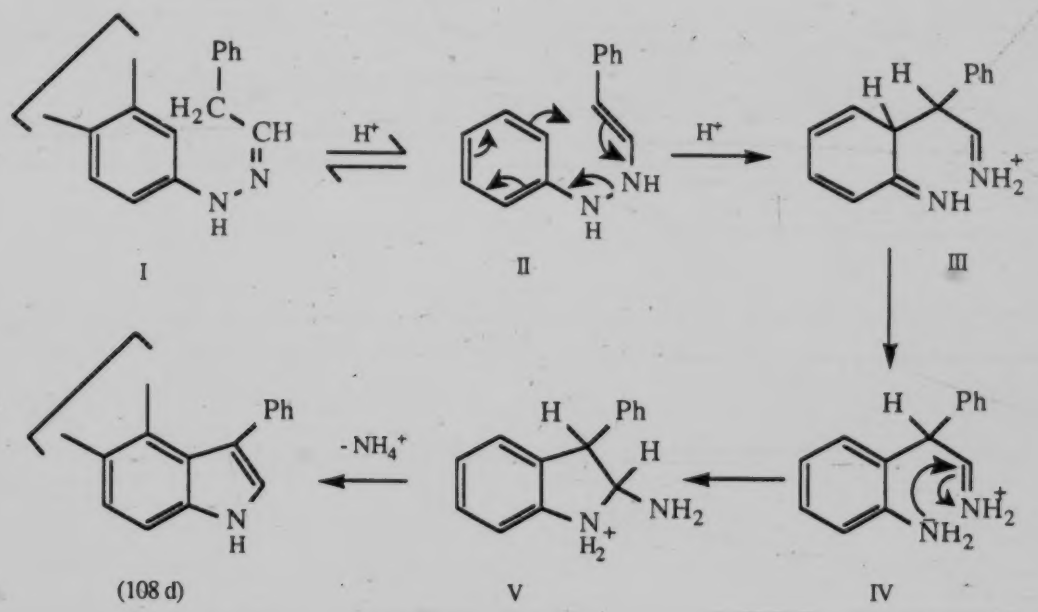


Fig. 45: Mechanism of formation of (108 d)

The key step in the reaction is a [3,3] sigmatropic rearrangement.[152] This proposed rearrangement is supported by ^{15}N labelling experiments which have shown that it is the nitrogen furthest from the ring that is eliminated as ammonia,[153] and by the isolation of characteristic intermediates.[154,155] The main function of the catalyst seems to be to speed the conversion of I to II (Fig. 45). The reaction can be performed without a catalyst.

The structures of the indoles (108 a-f) were confirmed from spectral data. For example, the ^1H nmr spectrum (δ) of (108 a) exhibited two doublets (J=8.53 Hz) at 7.36 and 7.9, assigned to C_5-H and C_4-H respectively. The doublet of doublets at 7.58 (J=7.90, 4.58 Hz) was due to C_9-H, while the broad singlet at 7.42 was due to C_2-H. Two doublet of doublets at 8.66 (J=7.90, 2.00 Hz) and 8.78 (J=4.58, 2.00 Hz) were assigned to C_{10}-H and C_8-H respectively. The C-1, methyl hydrogens appeared as a singlet (3H) at 2.72. The low field singlet (1H) at 11.51 was exchangeable with D_2O, and assigned to N-H. The ir spectrum (cm^{-1}) showed absorptions at 3189 (N-H) and 1655 (C=O), while the high resolution mass spectrum exhibited a molecular ion corresponding to $C_{15}H_{10}N_2O_2$: Mass calculated, 250.0742 ; mass found, 250.0740.

6.5. FIVE MEMBERED RING WITH 1 OXYGEN:

Benzimidazoles (e.g. 90, 94, 99), benzotriazoles (e.g. 100), benzothiazoles (e.g. 103, 105) and indoles (108 a-f) all contained rings with one or more nitrogen atoms. Pharmacological test results revealed that some of these were good lipoxygenase inhibitors (e.g. 90, 94, 99, 108 a), while others (e.g. 105) were dual inhibitors. To derive structure activity relationships it was necessary to synthesize ring systems which did not contain nitrogen. Benzofurans (e.g. 113, 114) were the obvious choice.

6.5.1. Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11(11H)-one:

Demethylation of 7-methoxy-1-azaxanthone (73d) was done by refluxing (73d) with 48% hydrobromic acid for 6 hours. The resulting 7-hydroxy-1-azaxanthone (109) was converted to the potassium phenolate salt with potassium carbonate and reacted with allyl bromide. This afforded 7-allyloxy-1-azaxanthone (110) in good yield (98%). Claisen rearrangement of (110) resulted in the formation of 6-allyl-7-hydroxy-1-azaxanthone (111).[156] Cyclization of azaxanthone (111) under strong acidic conditions led to the formation of the dihydrobenzofuran (112). Refluxing (112) with N-bromosuccinimide in

carbon tetrachloride resulted in the benzylic bromination of (112) and immediate *in situ* dehydrobromination to form benzofuran (113) (Fig. 46).

Allyl aryl ethers when heated, rearrange to o-allyl phenols in Claisen rearrangements.[157] If both ortho positions are filled the allyl group migrates to the para position. Migration to the meta position has not been observed. In the ortho migration the allyl group always undergoes an allylic shift. That is as shown in Fig. 47, a substituent α

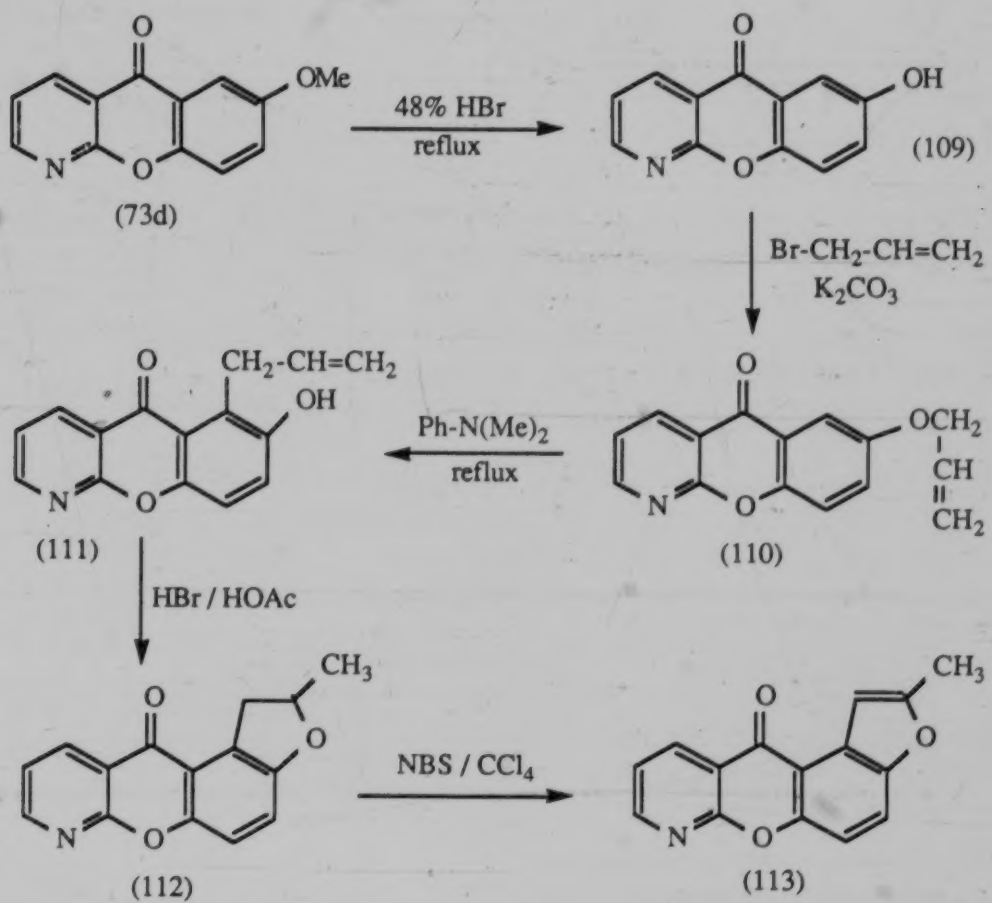


Fig. 46: Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11(11H)-one.

to the oxygen is now γ–to the ring(and vice versa). On the other hand, in the para migration there is never an allylic shift. The allyl group is found exactly as it was in the original ether.

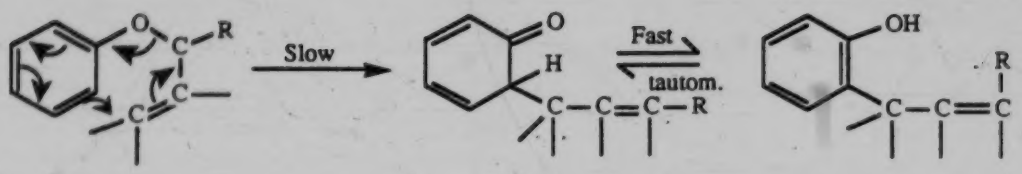


Fig. 47: Mechanism of Claisen rearrangement.

The mechanism involves a concerted pericyclic [3,3] sigmatropic rearrangement. In the Claisen rearrangement of 7-allyloxy-1-azaxanthone (110), the migration occurs solely to the C-6 position, probably due to the directing effect of the carbonyl group (section 6.1.1.).

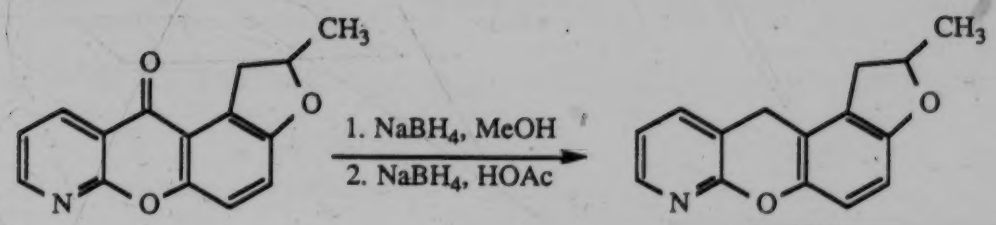
The reaction does not require a catalyst and the usual reaction temperature is around 200^0C. The aryl ether is heated either alone or in boiling dimethylaniline (b.p 193^0C) or diethylaniline (b.p 215^0C). Ring substituents have little influence on the reaction.

The ^{1}H nmr spectrum (δ) of benzofuran (113) exhibited a 3H singlet at 2.6 due to the C-2 methyl group. The 3H multiplet at 7.48 was attributed to C_1-H, C_9-H and C_5-H. The doublet at 7.82 (J=8.91 Hz) was assigned to C_4-H. At 8.78 the absorptions of C_8-H and C_{10}-H overlapped to appear as a multiplet. The ir spectrum (cm^{-1}) exhibited an absorption at 1655 (C=O), while the high resolution mass spectrum displayed a molecular ion corresponding to $C_{15}H_9NO_3$: Mass calculated, 251.0582 ; mass found, 251.0568.

6.5.2. Synthesis of 2-methylpyrido[3',2':5,6]pyrano[3,2-e](11H)1,2-dihydrobenzofuran:

Two step reduction of dihydrobenzofuran (112) with sodium borohydride in methanol and sodium borohydride in acetic acid afforded dihydrobenzofuran (114) in moderate yield (80%). A similar reduction of benzofuran (113) was not successful.

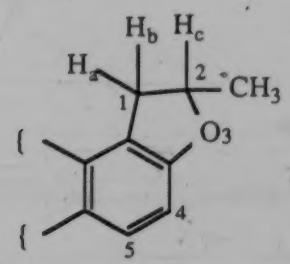
The ^{1}H nmr spectrum (δ) of (114) exhibited a 3H doublet (J=6.45 Hz) at 1.5, attributed to the C-2 methyl group. The doublet of doublets at 2.72 and at 3.22 were assig-



(112) (114)

Fig. 48: Two step synthesis of dihydrobenzofuran (114).

ned to the C-1 methylene protons. This splitting pattern of methylene hydrogens can be attributed to the asymmetric centre at C-2. The two methylene protons (H_a and H_b) are not equivalent. Each proton is split by the other (J_{gem}=15.31 Hz) and unequally by the proton on the assymmetric carbon (H_c) (J=7.65 and 8.93 Hz). The 2H singlet at 3.92 was due to the C-11 methylene group. The 1H multiplet at 4.86 was assigned to C_2-H (H_c) on the asy-



(114)

mmetric carbon. It is split by the C-2 methyl protons as well as C-1 protons. The two doublets at 6.6 and 6.9 (J=8.63 Hz) were assigned to C_5-H or C_4-H. Since each proton is next to an oxygen atom it is difficult to make exact assignments in this case. The three doublet of doublets at 8.14 (J=4.55, 2.15 Hz), 7.50 (J=7.19, 2.15 Hz) and 7.0 (J=7.19, 4.55 Hz) were attributed to C_8-H, C_{10}-H and C_9-H respectively. The ir spectrum (cm^{-1}) exhibited absorptions at 2984(C-H) and 1581 (C=C), while the high resolution mass spectrum showed a molecular ion corresponding to $C_{15}H_{13}NO_2$: Mass calculated 239.0946 ; mass found, 239.0934.

6.5.3. Synthesis of 2-aminopyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11(11H)-one:

7-Hydroxy-1-azaxanthone (109) was dissolved in a mixture of concentrated hydrochloric acid and concentrated sulfuric acid (2 : 1) containing paraformaldehyde. A gentle stream of hydrochloric acid gas was passed through the reaction mixture and the greenish precipitate which formed was filtered. The ^1H nmr spectrum of the crude product

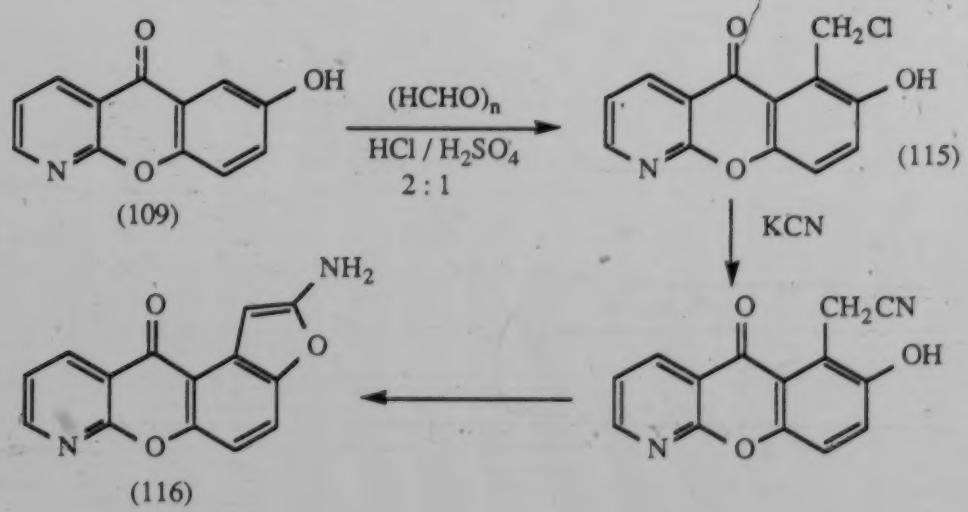


Fig. 49: Synthesis of 2-aminopyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11-one.

indicated that the chloromethyl group was located at the C-6 position. The product (115) was then used in the next step without further purification. Refluxing with potassium cyanide in a dioxane / water mixture afforded the reddish brown, 2-aminobenzofuran (116) (Fig. 49).

The CH_2Cl group is introduced into certain aromatic compounds when they are treated with formaldehyde and hydrochloric acid gas. This chloromethylation[158] reaction is greatly facilitated by activating groups like alkyl, alkoxy and hydroxy and hindered by deactivating groups. 1-Azaxanthone does not react to give a chloromethylated product probably due to deactivation by the C-5 carbonyl. 1-Azaxanthene, on the other hand undergoes chloromethylation to give 7-chloromethyl-1-azaxanthene (section 3.3.2.4).

Reagents like chloromethyl ether and dichloromethyl ether have also been used for chloromethylation. Since these are especially hazardous, attempts have been made to develop alternate reagents. One such attempt[159] describes the use of methoxyacetyl chloride and aluminum chloride in nitromethane or carbon disulfide.

The ^1H nmr spectrum (δ) of 2-aminobenzofuran (116) exhibited a singlet at 6.32 due to C_1-H. Two doublets at 7.05 and 7.72 (J=7.99 Hz) were attributed to C_5-H and C_4-H, respectively. The broad singlet at 7.2 was exchanged with D_2O and assigned to the NH_2 protons.Three doublet of doublets at 7.62 (J=7.74, 4.49 Hz), 8.66 (J=7.74, 2.00 Hz) and 8.82 (J=4.49, 2.00 Hz) were attributed to C_9-H, C_{10}-H and C_8-H respectively. The ir spectrum (cm^{-1}) showed absorptions at 3468, 3361 (NH_2) and 1646 (C=O), while the high resolution mass spectrum exhibited a molecular ion corresponding to $C_{14}H_8N_2O_3$: Mass calculated, 252.0534 ; mass found, 252.0544.

6.6. FIVE MEMBERED RINGS WITH OXYGEN AND NITROGEN:

Benzofurans (e.g. 112, 113, 114 and 116) were generally inactive or less active compared to benzimidazoles, benzothiazoles and indoles (e.g. 94, 99, 105). As a next step in our studies it was proposed to synthesize compounds with five membered rings containing both oxygen and nitrogen. Benzoxadiazole (120) and benzoxazole (121) belong to this series.

6.6.1. Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]benzoxadiazol-11(11H)-one:

Nitration of 7-methoxy-1-azaxanthone (73d) afforded the expected product 7-methoxy-6-nitro-1-azaxanthone (117). Demethylation of (117) was carried out by refluxing with 48% hydrobromic acid, to give 7-hydroxy-6-nitro-1-azaxanthone (118). Reduction with 10% palladium-charcoal and hydrazine resulted in the formation of 6-amino-7-hydro-

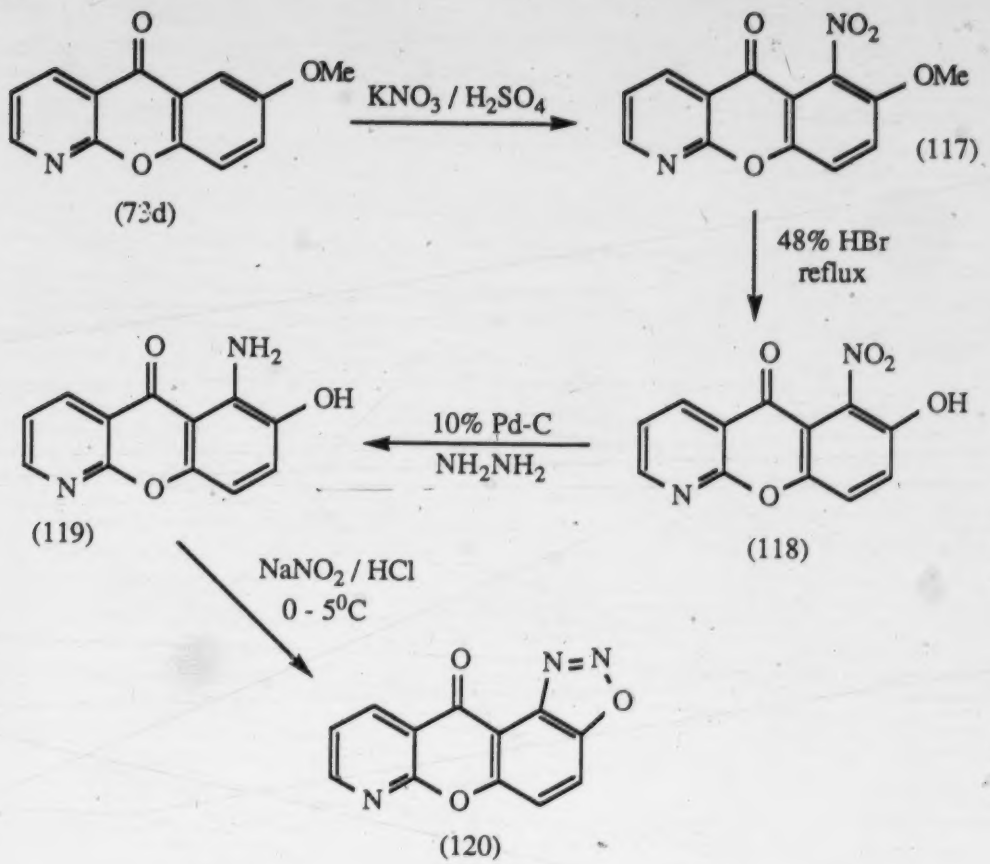


Fig. 50: Synthesis of pyrido[3',2':5,6]pyrano[3,2-e]benzoxadiazol-11(11H)-one.

xy-1-azaxanthone (119). This reduction was selective in that it did not reduce the pyridine ring (section 4.1.).

Diazotization of 6-amino-7-hydroxy-1-azaxanthone using sodium nitrite in conc. HCl afforded benzoxadiazole (120) in good yield (78%) (Fig.50).

The ^1H nmr spectrum (δ) of (120) displayed two doublets at 7.18 and 7.92 (J=9.84 Hz), assigned to C_5-H and C_4-H respectively. The C_9-H appears as a doublet of doublets (J=8.02, 4.66 Hz) at 7.72, while two doublet of doublets at 8.76 (J=8.02, 2.59 Hz) and 8.9 (J=4.66, 2.59 Hz) were due to C_{10}-H and C_8-H, respectively. The ir spectrum (cm^{-1}) exhibited absorptions at 2125 (N=N), 1670 (C=O) and 1600 (C=C) while the high

resolution mass spectrum displayed a molecular ion corresponding to $C_{12}H_5N_3O_3$: Mass calculated, 239.0330 ; mass found, 239.0326.

6.6.2. Synthesis of 2-mercaptopyrido[3',2':5,6]pyrano[3,2-e]benzoxazol-11(11H)-one:

Reaction of 6-amino-7-hydroxy-1-azaxanthone with potassium ethylxanthate affords 2-mercaptobenzoxazole (121) in low yield (35%). Potassium ethylxanthate was prepared by adding carbon disulfide to potassium hydroxide dissolved in ethanol.[160]

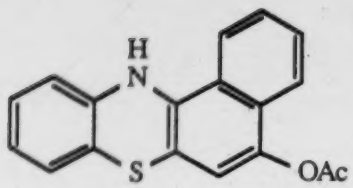
(119) (121)

Fig. 51: Synthesis of 2-mercaptopyrido[3',2':5,6]pyrano[3,2-e]benzoxazol-11(11H)-one.

The ^1H nmr spectrum (δ) of 2-mercaptobenzoxazole (121) displays two ortho coupled doublets at 7.56 and 8.0 (J= 8.73 Hz), due to C_5-H and C_4-H respectively. At 7.64 is a doublet of doublets (J=7.71, 4.86 Hz) assigned to C_9-H. The doublet of doublets at 8.65 (J=7.71, 1.7 Hz) was due to C_{10}-H, while the broad doublet at 8.84 (J=4.80 Hz) was attributed to C_8-H. The ir spectrum (cm^{-1}) exhibited absorptions at 2360 (S-H) and 1655 (C=O). The microanalytical data (± 0.4%) also confirmed the molecular formula of $C_{13}H_6N_2O_3S$.

6.7. SIX MEMBERED RINGS:

Benzophenothiazine derivatives have been reported to be potent leukotriene inhibitors.[161] Compound (122) decreases dyspnea symptoms (ED_{50} = 4mg/kg i.p) in asthmatic rats sensitized with egg albumin. It was reported to be useful for treatment of allergic conditions, asthma, cardiovascular disorders, inflammation and pain. Therefore it

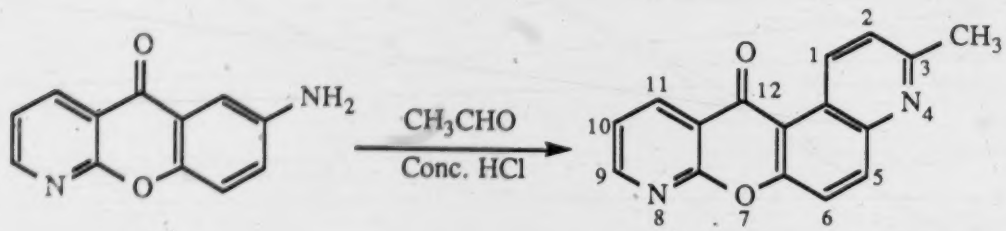


(122)

was proposed to synthesize six membered rings across C-6,7 of 1-azaxanthone. Quinoline (123), benzodioxane (124) and dihydrobenzoxazine (126) were synthesized under this category.

6.7.1 Synthesis of 3-methylpyrido[3',2':5,6]pyrano[3,2-f]quinolin-12(12H)-one.

The reaction of 7-amino-1-azaxanthone (73c) with acetaldehyde in concentrated hydrochloric acid, under reflux, afforded the quinoline (123) in moderated yields of up to 55% (Fig. 52).



(73c) (123)

Fig. 52: Synthesis of 3-methylpyrido[3',2':5,6]pyrano[3,2-f]quinolin-12(12H)-one.

This reaction utilizes the Doebner Von Miller procedure for the synthesis of quinoline, which itself is a modification of the Skraup quinoline synthesis.[162] In this process, a primary aromatic amine is heated in the presence of hydrochloric acid. The accepted mechanism involves self condensation of the aldehyde to give an α,β–unsaturated aldehyde which then reacts with the amine to form the quinoline (Fig. 53).

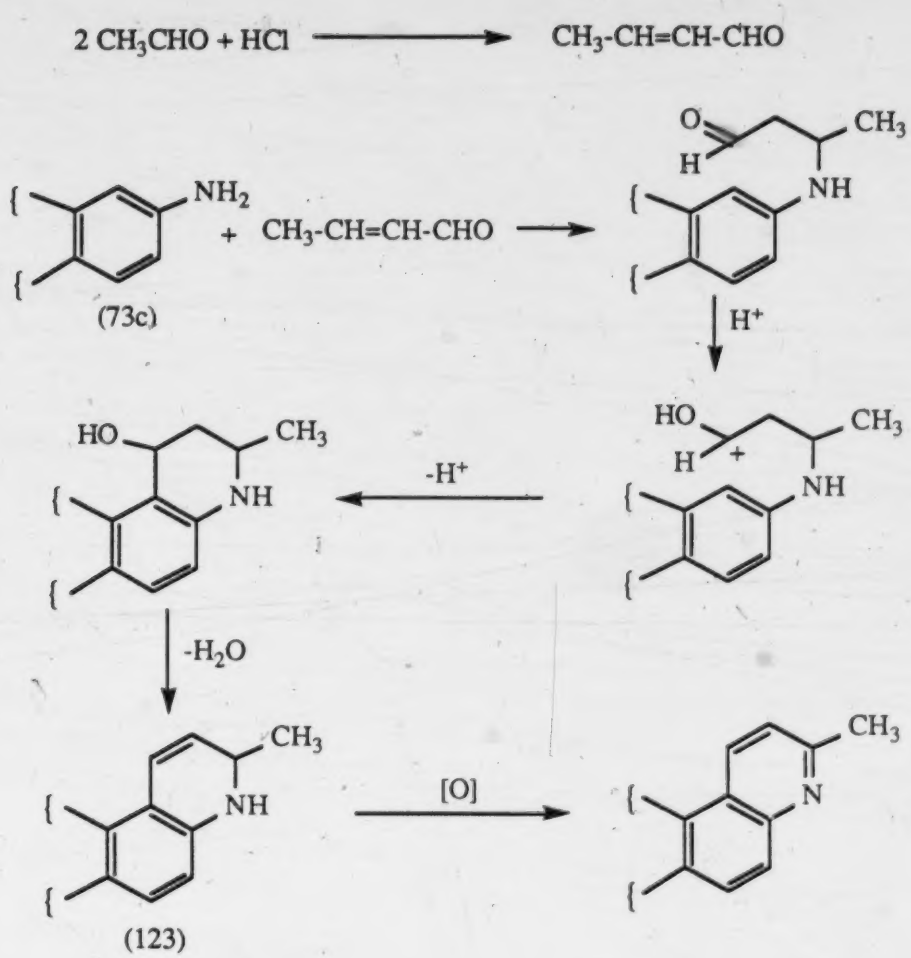
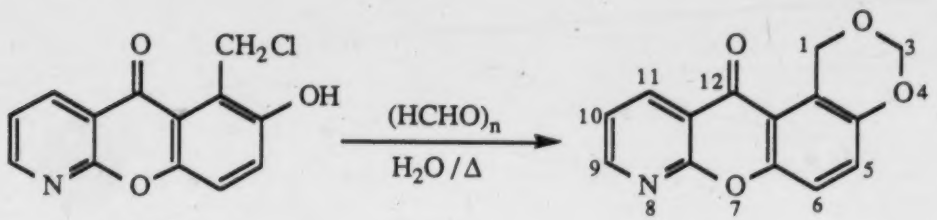


Fig. 53: Mechanism of formation of quinoline (123).

The ^1H nmr spectrum (δ) of quinoline (123) exhibited a 2H multiplet at 7.74, assigned to C_2-H and C_{10}-H. The two doublets at 8.1 and 8.42 (J=8.75 Hz) are attributed to C_6-H and C_5-H respectively. The two doublet of doublets at 8.78 (J=7.87, 2.84 Hz) and 8.84 (J=4.81, 2.84 Hz) are due to C_{11}-H and C_9-H respectively. The doublet (J=8.75 Hz) at low field of 10.1 δ was assigned to C_1-H. This deshielding effect is caused by the orientation of C_1-H in the deshielding zone of C-12 carbonyl. The ir spectrum (cm^{-1}) exhibited absorptions at 1655 (C=O) and 1605 (C=N). The microanalytical results were within ± 0.4% of calculated values.

6.7.2. Synthesis of pyrido[3',2:5,6]pyrano[3,2-f]1,3-benzodioxan-12(12H)-one:



(115) (124)

Fig. 54: Synthesis of benzodioxane (124).

Chloromethylation of 7-hydroxy-1-azaxanthone (109) afforded the chloromethyl derivative (115) (section 6.5.3). Reaction of (115) with paraformaldehyde in water resulted in the formation of benzodioxane derivative (124). The mechanism of its formation may be illustrated as shown in Fig. 55.

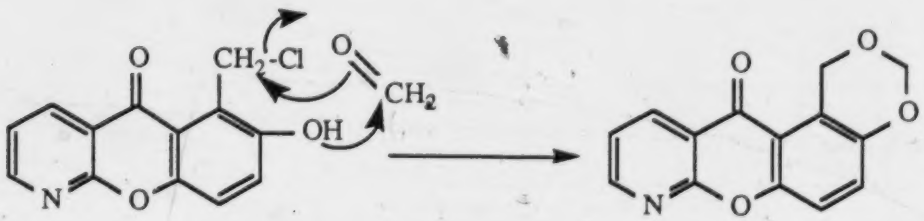


Fig. 55: Mechanism of formation of benzodioxane (124).

The ^1H nmr spectrum (δ) of benzodioxane (124) exhibits a 2H singlet at 5.32 due to C-1 hydrogens, while the 2H singlet slightly more down field at 5.54 was assigned to C-3 hydrogens, since they are flanked by two oxygen atoms. The doublet at 7.34 (J=9.7 Hz) was due to C_5-H or C_6-H and the multiplet at 7.48 was attributed to C_6-H or C_5-H and C_{10}-H. Two doublet of doublets at 8.64 (J=6.47, 3.23 Hz) and 8.78 (J=4.85, 3.23 Hz) were assigned to C_{11}-H and C_9-H respectively. The ir spectrum (cm^{-1}) exhibited absorptions at 2910 (C-H) and 1663 (C=O). The microanalytical values also confirmed the molecular formula of $C_{14}H_9NO_4$.

6.7.3. Synthesis of 2-hydroxy-2-hydrazinopyrido[3',2':5,6]pyrano[3,2-f]2,3-dihydro (1H)-1,4-benzoxazin-12(12H)-one :

7-Hydroxy-6-nitro-1-azaxanthone (118) was converted to its phenolate salt by refluxing with sodium carbonate in acetone and reacted with methyl bromoacetate, to give 7-methylacetoxy-6-nitro-1-azaxanthone (125). Azaxanthone (125) on refluxing with hydrazine and 10% palladium-charcoal in ethanol, afforded benzoxazine (126) in good

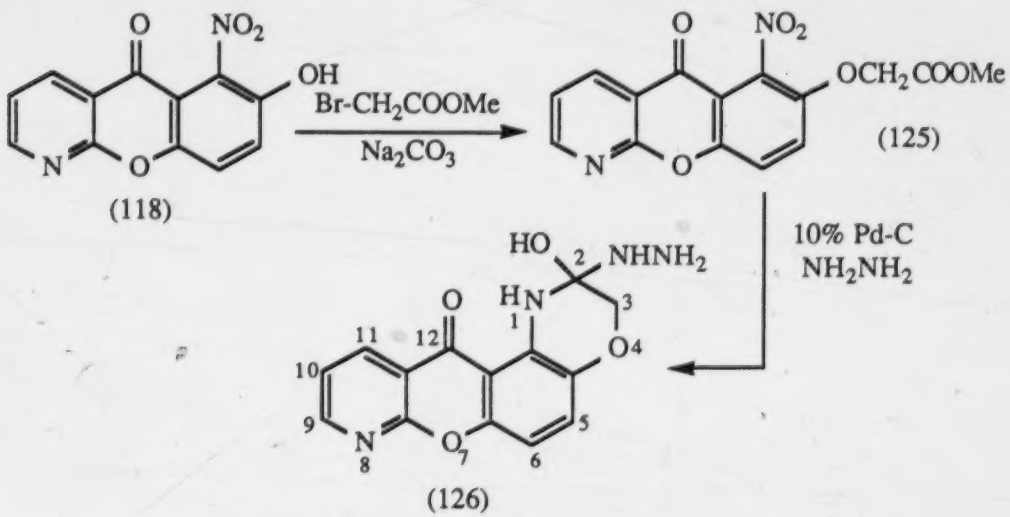


Fig. 56: Synthesis of dihydrobenzoxazine (126).

yield (85%). The mechanism of the reaction may be explained as shown in Fig.57. Nucleophilic attack of the hydrazine molecule on the ester group leads to the formation of the intermediate (A) which undergoes intramolecular cyclization to dihydrobenzoxazine (126). The ^1H nmr spectrum (δ) of dihydrobenzoxazine (126) displayed a broad singlet (5H) at 4.6, attributed to the overlapping of 3-CH_2, 2-$NHNH_2$ and 2-OH absorptions. D_2O exchange results in a single sharp peak integrating for two hydrogens. Two doublets at 6.62 and 7.3 (J=9.26 Hz) are due to C_5-H and C_6-H respectively. Three doublet of doublets at 7.52 (J=8.00, 5.89 Hz), 8.56 (J=8.0, 3.37 Hz) and 8.72 (J=5.89, 3.37 Hz)

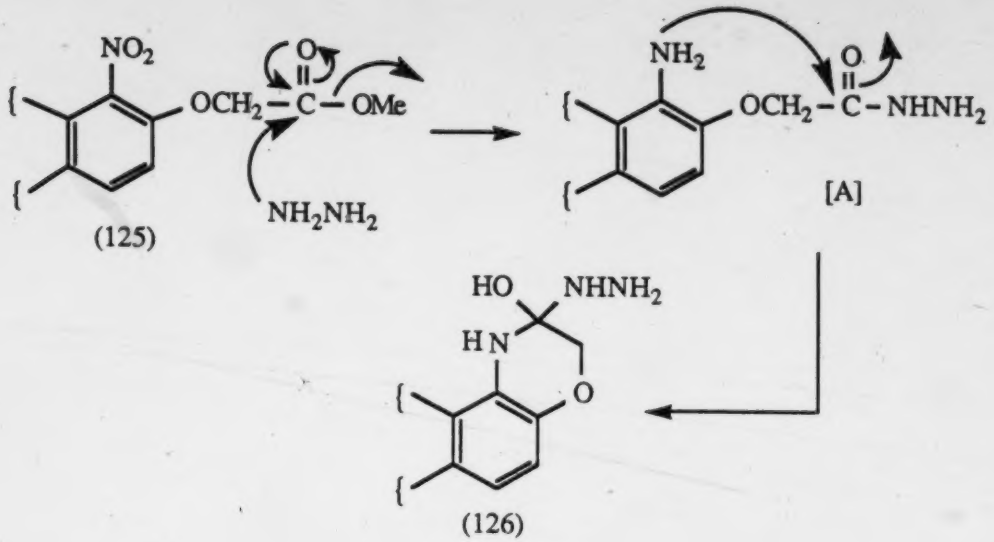
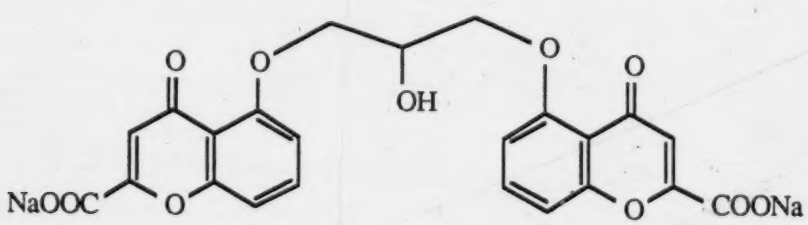


Fig. 57: Mechanism of formation of dihydrobenzoxazine (126).

are assigned to C_{10}-H, C_{11}-H and C_9-H, respectively. The downfield singlet at 9.68 was exchangeable with D_2O and assigned to N-H. The ir spectrum (cm^{-1}) exhibited absorptions at 3480, 3350 (br, OH, NH_2), 3290 (NH) and 1645 (C=O). The microanalytical values were within ($\pm$ 0.4%) of calculated values.

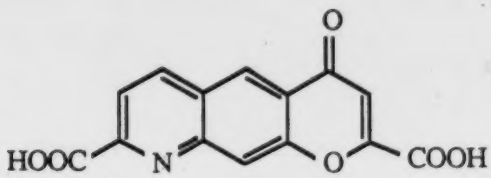
6.8. BENZOPYRONES:

The benzopyrone structure is widely associated with anti-allergic activity. For example, DSCG (127) is used in clinical practice for the prophylactic treatment of allergic diseases, especially asthma, rhinitis and conjunctivitis.[100]



(127)

Efforts have been made to improve duration of action, efficacy, oral absorption and potency over DSCG.[163] A number of anti-allergic pyranoquinoline dicarboxylic acid analogs of (128) were synthesized and found useful in the treatment of asthma. The benzopyrone derivative (132) synthesized in our laboratory has the azaxanthene structure



(128)

together with the benzopyrone structure, essential for anti-asthmatic activity, while compound (131) has structural similarity with L-649,923 (Merck Frost), a leukotriene receptor antagonist.[164]

6.8.1. Synthesis of 8-acetyl-7-hydroxy-5H-[1]benzopyrano[2,3-b]pyridine:

7-Methoxy-1-azaxanthone (73d) was converted to 7-methoxy-1-azaxanthene (129) by successive reductions with sodium borohydride in methanol and sodium borohydride in acetic acid. Demethylation of (129) with 48% hydrobromic acid afforded 7-hydroxy-1-azaxanthene (130). Friedel Crafts acylation of (130) with acetyl chloride and aluminum chloride, resulted in the exclusive formation of 8-acetyl-7-hydroxy-1-azaxanthene (131) (Fig. 58).

The 8-acetyl group in azaxanthene (131) is highly labile. Sodium borohydride reduction of (131) at room temperature, results in the elimination of the acetyl group and formation of 7-hydroxy-1-azaxanthene. Oxidation of azaxanthene (131) with sodium hypochlorite resulted in the elimination of the acetyl group along with chlorination of the benzene ring to yield 6,8-dichloro-7-hydroxy-1-azaxanthene. This reaction may be explained on the basis of formation of an o-hydroxy carboxylic acid. Aromatic o-hydroxy

carboxylic acids behave very similarly to β–oxo-carboxylic acids. These are known to lose CO_2 under mild conditions of heat (Fig. 59).[165]

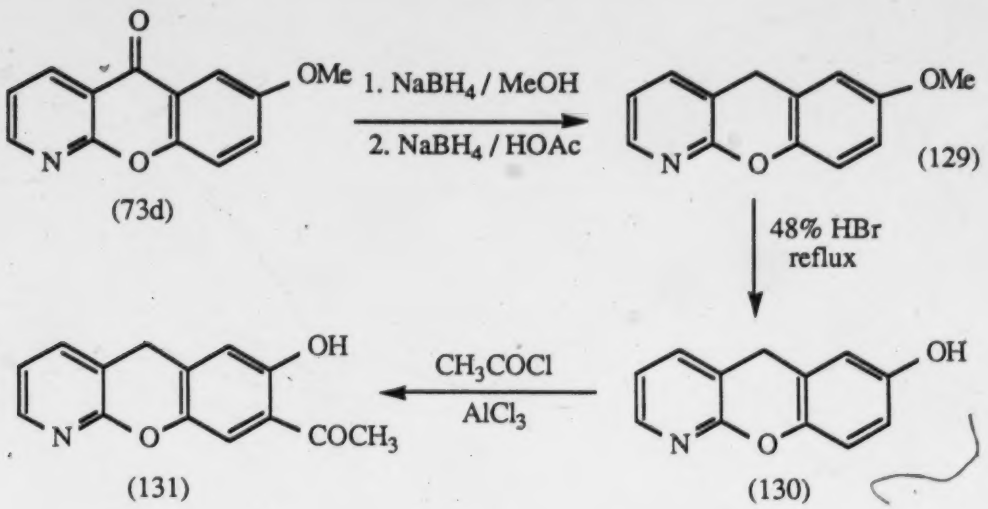


Fig. 58: Synthesis of 8-acetyl-7-hydroxy-5H-[1]benzopyrano[2,3-b]pyridine.

The ^1H nmr spectrum (δ) of azaxanthene (131) displayed two singlets at 2.62 (3H) and 4.1 (2H) due to C-8 acetyl hydrogens and C-5 methylene hydrogens, respectively. The C_6-H appears as singlet at 6.80, whereas C_9-H is merged with C_4-H and they appear as a multiplet at 7.54. The doublet of doublets at 7.06 (J=7.0, 4.85 Hz) was due to C_3-H,

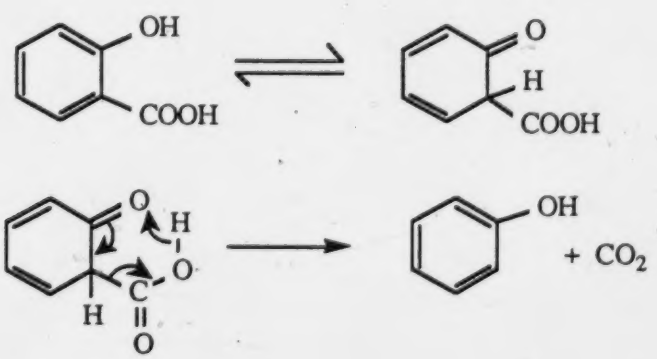


Fig. 59: Decarboxylation of an o-hydroxy carboxylic acid.

while the doublet at 8.2 (J=4.85 Hz) was attributed to C_2-H. The ir spectrum (cm^{-1}) displayed absorptions at 3468 (O-H) and 1753 (C=O). Microanalytical values : Calculated (found), C-69.69 (69.18) ; N-4.59 (4.39) ; H-5.80 (6.17). The high resolution mass spectrum exhibited a molecular ion corresponding to $C_{14}H_{11}NO_3$: Mass calculated, 241.0738 ; mass found, 241.0733.

6.8.2. Synthesis of 3-acetyl-2-methylpyrido[3',2':5,6]pyrano[2,3-g](4H,11H)benzo-4-pyrone:

Reaction of 8-acetyl-7-hydroxy-1-azaxanthene with freshly fused sodium acetate and acetic anhydride at 160^0C afforded the benzopyrone (132).

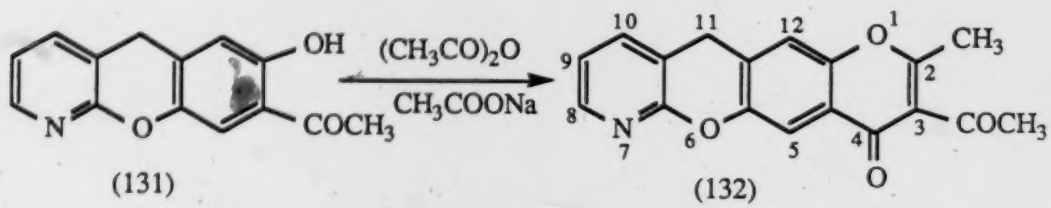


Fig. 60: Synthesis of benzopyrone (132).

o-Hydroxy ketones when heated with acid anhydrides in the presence of sodium or potassium salts of the corresponding acids form chromones, flavones or isoflavones. The most probable course of transformation, called the Kostanecki reaction[166,167] is shown in (Fig.61). The ester I undergoes rearrangement to the ketone II, which is acylated to yield the triketone intermediate III. This could undergo cyclization to the benzopyrone derivative (132).

The ^{1}H nmr spectra (δ) of benzopyrone (132) exhibited two 3H singlets at 2.54 and 2.66 attributed to 2-methyl and 3-acetyl protons, respectively. The 2H singlet at 4.27 was due to 11-methylene hydrogens, while the two singlets at 7.3 and 7.94 were assigned to C_{12}-H and C_5-H, respectively. The doublet of doublets at 7.1 (J=7.42, 4.54 Hz) was due to C9-H. Two doublets at 7.6 (br, J=7.42 Hz) and 8.27 (br, J=4.54 Hz) were attributed to

C_{10}-H and C_8-H, respectively. The ir spectrum (cm^{-1}) exhibited absorptions at 1696 ($C{=}OCH_3$) and 1630 (C=O), while the high resolution mass spectrum displayed a molecular ion corresponding to $C_{18}H_{13}NO_4$: Mass calculated, 307.0844 ; mass found, 307.0846.

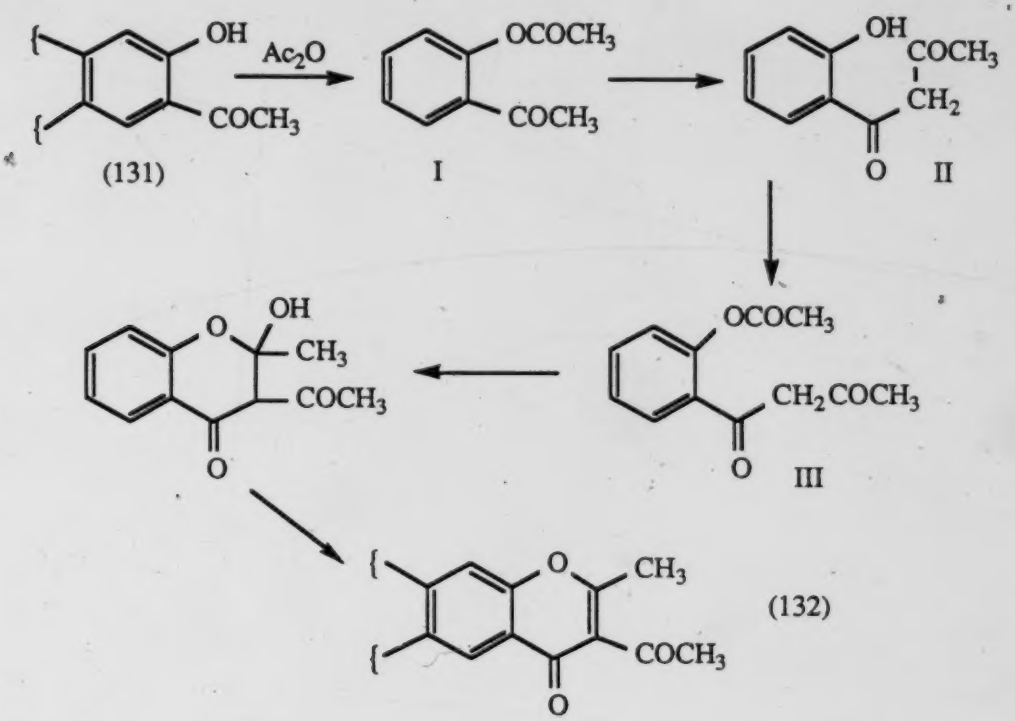


Fig. 61: Mechanism of formation of benzopyrone (132).

7.0. PHARMACOLOGICAL EVALUATION:

Pharmacological evaluation was conducted by Dr. John Burka, Department of Anatomy and Physiology, Atlantic Veterinary College, University of Prince Edward Island.

7.1. Model used:

The primary model used to screen potential lipoxygenase and cyclooxygenase inhibitors are the guinea pig spirally cut trachea and lung parenchyma strips.[75]

7.1.1. Effectiveness of the model :

Arachidonic acid is metabolised via the cyclooxygenase and lipoxygenase pathways to yield prostaglandins and leukotrienes, respectively. Arachidonic acid, when administered to guinea pig isolated trachea in the presence of indomethacin induces a pronounced contraction of the smooth muscle. This action has been shown to be due to the products produced by the lipoxygenase pathway, particularly peptido-lipid leukotrienes (LTC_4, LTD_4 and LTE_4).[168] In contrast, when arachidonic acid is administered to lung parenchymal strips, a good contraction is obtained in the absence, but not in the presence of indomethacin. Thus the arachidonic acid induced contractions of the parenchymal strips are largely due to the synthesis of cyclooxygenase products. Thus if a compound inhibits arachidonic acid induced contractions of indomethacin treated trachea, it means that the compound is either inhibiting the lipoxygenase pathway or blocking the receptor site of lipoxygenase. Similarly if a compound inhibits arachidonic acid-induced contractions of lung parenchymal strips, it means that the cyclooxygenase pathway is being blocked. Trial studies with known cyclooxygenase inhibitors e.g. indomethacin and known lipoxygenase inhibitors e.g. NDGA and a leukotriene receptor antagonist, L-649, 923 (Merck Frost), has confirmed that the model is working and that the sensitivity of inhibition was similar to that obtained with models using isolated enzymes.

7.1.2. **Procedure :**

In the initial secreen for a potential lipoxygenase inhibitor / leukotriene receptor antagonist, indomethacin (8.4 μM) was added to the organ baths containing trachea 45 minutes prior to challenge with arachidonic acid (66μM). The test compound (10^{-5}M) is added to the organ bath, 30 minutes prior to arachidonic acid. Because we have now found that many of our compounds are very potent , our initial screen for inhibition is now done with a lower concentration of the test compound (10^{-6}M). The resulting contraction over a 60 minutes period is compared to one from a paired tracheal strip in the absence of the test compound. If the drug inhibited the tracheal contractions by greater than 50%, further studies were carried out. Similar comparisons for cyclooxygenase inhibition were carried out using parenchymal strips, which were not treated with indomethacin.

If a test compound passed the initial screen, the pD_2 value (i.e. the negative log of the concentration that inhibited the arachidonic acid contraction by 50%) was determined. Results are presented in Table 4 (Section 7.2.) and compared to the lipoxygenase inhibitor, sodium meclofenamate, the leukotriene antagonist, L-649,927 and the cyclooxygenase inhibitor , indomethacin.

7.1.2.1. Test for bronchodilating activity:

During testing it was observed that several compounds had airway smooth muscle relaxing activity, even when added to tissues already relaxed with indomethacin. Controlled studies of test compounds as bronchodilators were compared to isoprenaline and L-649,923. Tracheal spirals and lung parenchyma strips were contratced with histamine (10^{-5} M) and cumulative concentration-response curves for each agent established. The maximal contraction obtainable for each tissue was determined by adding isoprenaline (10^{-6}M) after no further relaxation was attainable with the test compound.

7.2. Pharmacological results:

From (Table 4) it is evident that several compounds exhibited lipoxygenase inhibiting activity comparable to known lipoxygenase inhibitors e.g. NDGA, nafazatrom (Miles) and piriprost (Upjohn). In addition several compounds were dual inhibitors. Compound (105) with a pD_2 value of 7.68 (trachea) was up to 1000 times more potent than piriprost and nafazatrom. In addition it showed dual inhibition. Compounds which were dual inhibitors generally showed a pD_2 value of less than 5.0 in parenchyma (cyclooxygenase inhibition). This may suggest that the observed effect may be due to non-specific factors rather than selective cyclooxygenase inhibition.

The most potent compound (105) was studied further for bronchodilating activity in comparison with isoprenaline, L-649,923, forskolin and aminophylline (Table 5). The bronchodilating activity of compound (105) was less than that of isoprenaline, L-649,923 and forskolin, but much more than that of aminophylline. Compound (105) was almost 100-fold more potent as an inhibitor of the lipoxygenase pathway than as a bronchodilator.

This result is encouraging since bronchodilation is desirable in the treatment of asthma. Perhaps of even greater significance is the previously believed observation that indomethacin treated trachea was already at baseline-tone. The ability of compound (105) to further dilate trachea suggests that other substances, possibly leukotrienes, may also be contributing to tracheal tone. Further investigations are imperative.

Table 4: Inhibition of arachidonic acid induced contractions:

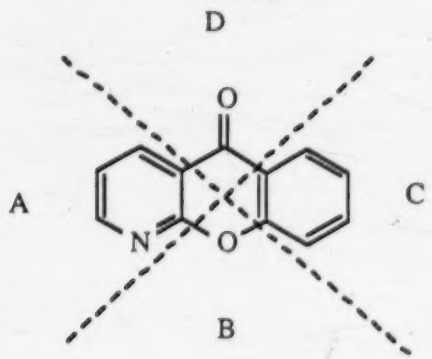
Comp. No.	pD_2 values Trachea	parenchyma
(90)	5.79 ± 0.33	-
(94)	5.75 ± 0.08	4.42 ± 0.20
(103)	4.74 ± 0.07	4.92 ± 0.19
(105)	7.68 ± 0.32	4.88 ± 0.10
(108 a)	5.82 ± 0.27	4.48 ± 0.23
(112)	-	-
(113)	-	-
(114)	-	-
(116)	-	-
(121)	-	-
(123)	>50% inhibition at 10^{-6}M	-
(131)	5.63 ± 0.25	4.49 ± 0.09
(132)	5.91 ± 0.33	highly variable
(80 k)	4.14 ± 0.07	highly variable
(74 f) acid	-	-
Indomethacin	-	5.26 ± 0.37
Sod. meclofenamate	5.80 ± 0.19	6.28 ± 0.53
NDGA	5.31 ± 0.18	-
Nafazatrom	4.15	-
Piriprost	4.68	-
BW 755C	-	-
L-649, 923	6.48 ± 0.37	4.49 ± 0.19

Table 5: Bronchodilating activity

Compound No.	pD_2 values Trachea	Parenchyma
(105)	5.79 ± 0.13	5.13 ± 0.32
Forskolin	6.01	-
Aminophylline	4.13	-
L-649,923	6.06 ± 0.15	6.92 ± 0.27
Isoprenaline	7.54 ± 0.05	6.96 ± 0.10

- Inactive ; pD_2 values are mean ± SEM of the -ve logarithms

7.3. Proposed structure activity relationships for a lipoxygenase and / or dual inhibitors:



Modifications to the 1-azaxanthone molecule was carried out in four quadrants (A, B, C and D) as shown above.

Reduction of the pyridine ring to a tetrahydropyridine derivative (e.g. 74 f) results in the loss of activity. This suggests that two aromatic rings are essential for activity.

A tricyclic hydrophobic nucleus appears to be a requirement for activity. Ring opening at the oxygen bridge (80 k), reduces activity. A similar observation has been reported for structurally related anti-anaphylactic azaxanthones.[105] It has also been shown that the conformational rigidity of a heteroatom bridge is necessary for activity in a series of anti-asthmatic azaxanthenes.[108] From work done by other personnel in our laboratory it was observed that replacement of bridge oxygen by sulfur or selenium, generally enhances the activity.[169]

C-7 substitution with nitrogen containing substituents confers varying degrees of activity. A heteroaromatic ring fused across C-6,7-positions, provides compounds which are more potent than those with a simple C-7 nitrogen containing substituent (e.g. 84, 85) (section 6.0). 2-Methylimidazole, 2-aminothiazole, 3-methylpyrrole and 2-methylpyridine rings (e.g. 90, 94, 103, 105, 108a, 123) are associated with good lipoxygenase inhibitory activity. Compounds with a triazole ring (e.g 100, 101, 102) are yet to be tested. These compounds are expected to be more potent (e.g. 86, 87) (section 6.0).[145] 2-Methylimidazole and triazole derivatives (99 and 102) have the heteroaromatic rings fused at the 7,8-positions of azaxanthone to give a linear tetracyclic molecule. A structurally similar quinazoline derivative has been reported to be a potent anti-allergic drug.[145] One of the common features in the above compounds (e.g. 90, 94, 103, 105, 108 a) is the presence of exchangeable NH protons. It is possible that these hydrogens interact with the receptor site through hydrogen bonding.

Five membered heterocyclic rings without nitrogen, across C-6,7 of 1-azaxanthone e.g. dihydrofuran (112, 114) and furan (113, 116) did not show appreciable activity. Compound (131) with a hydroxyl and an acetyl group on the benzene ring of 1-azaxanthene (structurally similar to L-694,923, a leukotriene receptor antagonist) showed moderate lipoxygenase inhibitory activity. Compound (132) with a benzopyrone structure seen in many antiasthmatic drugs (e.g. DSCG) also displayed moderate lipoxygenase inhibitory activity.

Reduction of the C-5 carbonyl group to the methylene group (e.g 105) resulted in an increase in lipoxygenase inhibition along with dual inhibition. A dramatic increase in activity can be seen by comparing (103) to (105). Reduction of the C-5 carbonyl to the alcohol, resulted in a decrease in activity.[170]

Due to the limited number of compounds tested so far, it is difficult to draw significant structure activity relationships. When the results of a number of compounds submitted for testing are obtained, it will help in suggesting more accurately the structural features needed for a lipoxygenase or a dual inhibitor incorporating the azaxanthone structure.

IV. EXPERIMENTAL

Melting points were obtained on a Thomas Hoover capillary apparatus and are uncorrected. The ir spectra (KBr disc) were recorded on a Nicolet 5DX fourier transform spectrometer or Perkin-Elmer 267 spectrometer. ^1H nmr spectra were determined for solutions of deuterochloroform or deuterodimethylsulfoxide or a mixture of the two solvents. ^1H nmr spectra were measured on a Bruker AM 300 fourier transform spectrometer using TMS as an internal standard. Mass spectra were obtained on an AEI MS-50 spectrometer. Exact mass measurements of molecular ions were used where elemental analyses were not within $\pm$0.4%. Elemental analyses were carried out on a Perkin-Elmer 240B analyser. Column chromatography was performed with 100-200 mesh silica gel. Tetrahydrofuran solvent was dried by refluxing with sodium metal and benzophenone.

8.0. General procedure for the synthesis of 5H-[1]benzopyrano[2,3-b]-1,2,3,4-tetrahydropyridin-5-ones (74 a-h):

A suspension of 5H-[1]benzopyrano[2,3-b]pyridin-5-one (73 a, 3.9 g, 20 mmol) in ethanol (100 ml) was shaken in a Parr hydrogenator with a hydrogen pressure of 50 psi in the presence of 5% palladium-charcoal (0.4 g) for 4 hr. The catalyst was collected on a filter and washed with hot ethanol to give the product (74 a) as colorless crystals and recrystallised from ethanol. Details of physical properties and spectral information are given in Tables 1 and 2.

8.1. 5-Oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-carboxylic acid (73h) :

7-Methyl-1-azaxanthone (73b) (1 g, 4.7 mmol) was dissolved in a mixture of 70 ml of glacial acetic acid and 10 ml of concentrated sulfuric acid. Sodium dichromate (4 g, 13.4 mmol) was added and the mixture refluxed for 12 hr. The color of the reaction mixture turned from orange to deep blue. The reaction mixture was poured into ice water

and the precipitated white solid was filtered, washed several times with water and dried. The product was recrystallized from methanol to give 1-azaxanthone-7-carboxylic acid (73h) as a white solid (yield 1.00 g, 88%). Mp 300^0C, lit mp 300^0C[108]; ir (KBr) (cm^{-1}) : 3500-2400 (COOH), 1690 (C=O from acid), 1660 (C=O) ; ^{1}H nmr (DMSO-d_6) δ : 7.66 (dd, 1H, C_3-H, J=7.4, 4.50 Hz), 7.8 (d, 1H, C_9-H, J=8.8 Hz), 8.3 (dd, 1H, C_8-H, J=8.8, 2.2 Hz), 8.62 (m, 2H, C_4-H & C_6-H), 8.85 (dd, 1H, C_2-H, J=4.50, 2.18 Hz) ; Microanalysis for $C_{13}H_7NO_4$: found (calc) C-64.70 (64.73), H-2.91 (2.92), N-5.88 (5.80).

8.2. 5-Oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid (78) :

7-Methyl-1-azaxanthone (4 g, 18.9 mmol) was dissolved in 100 ml of 1,2-dibromoethane by means of reflux. Bromine (1.11 ml, 21.6 mmol) was dissolved in 10 ml of 1,2-dibromoethane and added dropwise to the reaction mixture. The resulting mixture was refluxed for 6 hr and the solvent removed by vacuum distillation. To the residue was added, sodium cyanide (2 g, 40 mmol) dissolved in a mixture of 20 ml of water and 80 ml of dioxane and refluxed for 4 hr. Dioxane was removed by evaporation under vacuum using a rotary evaporator. The resulting suspension was poured into 400 ml of water and extracted four times with 200 ml portions of methylene chloride. The combined methylene chloride extracts were evaporated to dryness in a rotary evaporator, to give a reddish-brown oily residue. The residue was dissolved in a mixture of 20 ml of concentrated sulfuric acid, 20 ml of glacial acetic acid and 20 ml of water.The resulting solution was refluxed for 5 hr and poured into crushed ice (200 ml). A brown precipitate of 1-azaxanthone-7-acetic acid (78) which formed was collected by filtration. The precipitate was redissolved in 100 ml of 10% sodium hydroxide solution, washed 2-3 times with 50 ml portions of chloroform to remove impurities and then poured into crushed ice (150 ml). The resulting solution was acidified with 10% hydrochloric acid solution when a light brown precipitate formed was filtered, washed free of acid and recrystallized from ethanol,

dioxane mixture (3 : 1) (yield 2.50 g, 52%) ; mp 237^{0}C, lit mp 244^{0}C[107] ; ir (KBr) (cm^{-1}): 3400-2400 (br, COOH), 1710 (C=O, from acid), 1660 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 3.8 (s, 2H, CH_2), 7.64 (dd, 1H, C_3-H, J=7.58, 5.44 Hz), 7.75 (d, 1H, C_9-H, J=9.14 Hz), 7.86 (dd, 1H, C_8-H, J=9.14, 2.52 Hz), 8.1 (d, 1H, C_6-H, J=2.52 Hz), 8.68 (dd, 1H, C_4-H, J=7.58, 2.33 Hz), 8.86 (dd, 1H, C_2-H, J=5.44, 2.33 Hz) ; microanalysis for $C_{14}H_9O_4N$: found (calc), C-65.50 (65. 87), H-3.88 (3.55), N-5.48 (5.48).

8.3. General procedure for the synthesis of 3-(2-hydroxybenzoyl)-1-methyl-2(1H)-pyridinones (80 a, k, i, d, h) :

A mixture of 1-methylbenzopyrano[2,3-b]pyridinium iodide (1 g, 2.94 mmol) and sodium nitrite (0.2 g, 3.0 mmol) in methanol : water (9 : 1, 100 ml) was refluxed with stirring for 45 minutes. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was taken up in water and extracted with chloroform (3 x 20 ml). The combined extract was dried (Na_2SO_4), solvent removed and the product recrystallized from methanol (yield 0.64 g, 95%). Details of spectral and physical properties of compounds (80 a-k) are described in Table 3.

8.4. 5H-[1]Benzopyrano[2,3-b]pyridine (81):

1-Azaxanthen-5-ol (0.2 g, 1.0 mmol) was dissolved in 15 ml of glacial acetic acid and stirred at 0^{0}C. Sodium borohydride (0.1 g, 2.6 mmol) was added to the reaction mixture slowly over a period of 5-10 minutes. The reaction mixture was stirred for 45 min and poured into crushed ice (50 ml). A white precipitate of 1-azaxanthene (81) was filtered, washed with water, dried and recrystallized from methanol, water (yield 0.15 g, 80%) ; mp 175^{0}C ; ir (KBr) (cm^{-1}): 1600 (C=C) ; ^{1}H nmr ($CDCl_3$) δ : 4.12 (s, 2H, CH_2), 7.04-7.32 (m, 5H, C_3, C_6, C_7, C_8 and C_9-H), 7.58 (m, 1H, C_4-H), 8.24 (m, 1H, C_2-H) ; microanalysis for $C_{12}H_9ON$: found (calc) : C-78.41 (78.66), H-4.99 (4.95), N-7.59 (7.64).

8.5. 6,6'-Dinitro-7,7'-dimethyl-5,5'-bi-1-azaxanthen (83):

Freshly cut sodium metal (0.2 g, 8.6 mmol) was allowed to react with 60 ml of 98% ethanol to form sodium ethoxide. To this solution, 7-methyl-6-nitro-1-azaxanthene (0.2 g, 0.826 mmol) was added and refluxed for 1 hr. The color of the solution turned dark blue, indicating the formation of the radical anion. The reaction was allowed to cool (the color turned to orange) and the ethanol was evaporated *in vacuo* . To the residue 50 ml of water was added and stirred. The undissolved portion was filtered, dried and recrystallized from methanol, THF to give the dimer (83) (0.30 g, 77%) ; mp 286^{0}C ; ir (KBr) (cm^{-1}): 1532, 1350 (NO_2); ^{1}H nmr ($CDCl_3$) δ: 2.42 (s, 3H, 7-CH_3), 4.58 (s, 1H, C_5-H), 6.60 (dd, 1H, C_4-H, J=7.46, 1.93 Hz), 6.82 (dd, 1H, C_3-H, J=7.46, 4.98 Hz), 7.02 (d, 1H, C_9-H, J=8.29 Hz), 7.30 (d, 1H, C_8-H, J=8.29 Hz), 8.24 (dd, 1H, C_2-H, J=4.98, 1.93 Hz) ; microanalysis for $C_{26}H_{18}N_4O_6$: found (calc) C-64.54 (64.72), H-3.70 (3.76), N-11.96 (11.61) ; chemical ionization mass spectra (NH_3) : (M+1) = 483 ; molecular weight = 482.

8.6. 7-Acetamido-5H-[1]benzopyrano[2,3-b]pyridin-5-one (73e):

Acetic anhydride (1.0 ml) was added to a hot stirred solution of 7-amino-1-azaxanthone (1.0 g, 4.7 mmol) in glacial acetic acid (25 ml) and heated on a water bath while stirring. The product which crystallized from solution was filtered, washed with water (3 x 20 ml) and dried. Dilution of the mother liquor with water afforded a second crop. Total yield of 7-acetamido-1-azaxanthone (73e) as yellow crystals was 1.05g (88%). Mp 297^{0}C ; ir (KBr) (cm^{-1}): 3345 (NH), 1686 (C=O), 1648 (NHC=O) ; ^{1}H nmr (DMSO-d_6/$CDCl_3$) δ : 2.10 (s, 3H, CH_3) ; 7.56 (dd, 1H, C_3-H, J=7.68, 4.54 Hz), 7.62 (d, 1H, C_9-H, J=9.13 Hz), 8.06 (dd, 1H, C_8-H, J=9.13, 2.44 Hz), 8.45 (d, 1H, C_6-H, J=2.44 Hz), 8.64 (dd, 1H, C_4-H, J=7.68, 1.75 Hz), 8.78 (dd, 1H, C_2-H, J=4.54, 1.75 Hz), 10.62 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{10}N_2O_3$: found (calc) C-66.07 (66.14), H-3.92 (3.96), N-11.01 (11.02).

8.7. 7-Acetamido-6-nitro-5H-[1]benzopyrano[2,3-b]pyridin-5-one (88):

A solution of KNO_3 (1.4 g, 13.8 mmol) in conc. H_2SO_4 (5 ml) was added dropwise to a solution of 7-acetamido-1-azaxanthone (73e) (2.0 g, 7.9 mmol) in conc. H_2SO_4 (15 ml) at 0^0C. The reaction was slowly returned to room temperature, stirred for 3 hr and poured into crushed ice (200 ml). The solid which precipitated was filtered, washed with water several times, washed with aqueous ammonia and again washed with excess water. The product was recrystallised from THF to give 7-acetamido-6-nitro-1-azaxanthone (88) as yellow crystals (1.50 g, 64%). Mp 280^0C ; ir (KBr) (cm^{-1}): 3386 (NH), 1640 (NH-C=O), 1667 (C=O), 1555 and 1374 (NO_2) ; ^{1}H nmr (DMSO-d_6/$CDCl_3$) δ : 2.10 (s, 3H, CH_3), 7.63 (dd, 1H, C_3-H, J=7.80, 4.60 Hz), 7.95 (d, 1H, C_9-H, J=8.97 Hz), 8.17 (d, 1H, C_8-H, J=8.97 Hz), 8.60 (dd, 1H, C_4-H, J=7.80, 2.00 Hz), 8.85 (dd, 1H, C_2-H, J=4.60, 2.0 Hz), 10.00 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_9N_3O_5$: found (calc) C-55.99 (56.19), H-3.02 (3.03), N-13.96 (14.04).

8.8. 7-Acetamido-6-amino-5H-[1]benzopyrano[2,3-b]pyridin-5-one (89):

To a hot solution of 7-acetamido-6-nitro-1-azaxanthone (0.5 g, 1.7 mmol) in acetone (100 ml) and 30% aqueous ammonia solution (50 ml), was added a solution of ferrous sulfate (5 g, 17.9 mmol) in aqueous ammonia (50 ml). The reaction mixture was heated on a water bath for 1.5-2 hr. This was then cooled and extracted with ethyl acetate (3x50 ml), dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The product was recrystallized from acetonitrile, to afford 7-acetamido-6-amino-1-azaxanthone (89) as yellow crystals (0.3 g, 67%). Mp 240^0C ; ir (KBr) (cm^{-1}): 3451, 3320, 3254 (NH_2, NH), 1639 (NHC=O), 1655 (C=O) ; ^{1}H nmr (DMSO-d_6/$CDCl_3$) δ : 2.11 (s, 3H, CH_3), 6.68 (d, 1H, C_9-H, J=8.72 Hz), 7.56 (m, 4H, C_8-H, C_3-H, NH_2, exch.), 8.57 (dd, 1H, C_4-H, J=7.92, 2.28 Hz), 8.7 (dd, 1H, C_2-H, J=4.36, 2.28 Hz), 9.02 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{11}N_3O_3$: found (calc) C-62.03 (62.45), H-4.10 (4.12), N-15.56 (15.61).

8.9. 2-Methylpyrido[3',2':5,6]pyrano[3,2-e]benzimidazol-11(1H,11H)-one (90):

A solution of 7-acetamido-6-amino-1-azaxanthone (89) (0.5 g, 1.9 mmol) in conc. HCl : ethanol (2 :1, 25 ml) was refluxed for 8 hr. After cooling, ethanol was removed *in vacuo* and the solution basified with aqueous ammonia. The mixture was extracted with ethyl acetate (3x20 ml), dried (Na_2SO_4) and concentrated. The resulting residue was then treated with acetone (5 ml). The insoluble portion was filtered, washed with cold acetone and recrystallized from acetonitrile to give benzimidazole (90) as tan crystals (0.30g, 65%). Mp 318^{0}C ; ir (KBr) (cm^{-1}): 3435 (NH), 1652 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 2.62 (s, 3H, CH_3), 7.5 (d, 1H, C_5-H, J=8.73 Hz), 7.67 (dd, 1H, C_9-H, J=7.78, 4.55 Hz), 8.09 (d, 1H, C_4-H, J=8.73 Hz), 8.75 (dd, 1H, C_{10}-H, J=7.78, 2.09 Hz), 8.89 (dd, 1H, C_8-H, J=4.55, 2.09 Hz), 12.99 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_9N_3O_2$: found (calc) C-66.60 (66.93), H-3.68 (3.61), N-16.59 (16.72).

8.10. 7-Acetamido-6-nitro-5H-[1]benzopyrano[2,3-b]pyridin-5-ol (91):

7-Acetamido-6-nitro-1-azaxanthone (88) (0.5 g, 1.67 mmol) was added to 150 ml of methanol and stirred at room temperature. Sodium borohydride (0.25 g, 6.68 mmol) was added to the reaction mixture in small quantities and the reaction was followed by TLC ($CHCl_3$: MeOH, 9 : 1). Completion of the reaction was indicated by the formation of a pale green colored solution. Methanol was then evaporated *in vacuo* and to the remaining residue was added cold water and the insoluble solid separated by filtration. The product was recrystallized from methanol to give 7-acetamido-6-nitro-1-azaxanthen-5-ol (0.45 g, 75%). Mp 258^{0}C ; ir (KBr) (cm^{-1}): 3246 (br, OH, NH), 1540 and 1333 (NO_2) ; ^{1}H nmr (DMSO-d_6) δ: 2.13 (s, 3H, CH_3), 6.16 (d, 1H, C_5-H, J=8.01 Hz), 6.5 (d, 1H, C_5-OH, J=8.01 Hz), 7.34 (dd, 1H, C_3-H, J=7.46, 5.24 Hz), 7.46 (d, 1H, C_9-H, J=8.56 Hz), 7.64 (d, 1H, C_8-H, J=8.56 Hz), 8.08 (dd, 1H, C_4-H, J=7.46, 1.65 Hz), 8.36 (dd, 1H, C_2-H, J=5.24, 1.65 Hz), 9.9 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{11}N_3O_5$: found

(calc) C-54.94 (55.81), H-3.61 (3.65), N-14.18 (13.95) ; high resolution mass spectrum: calculated 301.0698, found 301. 0696.

8.11. 7-Acetamido-6-nitro-5H-[1]benzopyrano[2,3-b]pyridine (92):

7-Acetamido-6-nitro-1-azaxanthen-5-ol (91) (0.5 g, 1.66 mmol) was dissolved in 10 ml of trifluoroacetic acid and stirred at 0^0C under an atmosphere of nitrogen. Sodium borohydride (0.15 g,3.9 mmol) was added to the reaction mixture portionwise over a period of 15 min. The reaction mixture was stirred for 0.5 hr while allowing it to slowly return to room temperature and then poured into crushed ice (100 ml). The precipitate which formed was filtered and recrystallized from ethanol to give 7-acetamido-6-nitro-1-azaxanthene (0.40 g, 85%). Mp 245^0C ; ir (KBr) (cm^{-1}): 3238 (NH), 1662 (NHC=O), 1537 and 1368 (NO_2) ; ^1H nmr (DMSO-d_6) δ: 2.1 (s, 3H, CH_3), 4.18 (s, 2H, CH_2), 7.18 (dd, ^1H, C_3-H, J=7.24, 4.42 Hz), 7.37 (d, 1H, C_9-H, J=8.85 Hz), 7.46 (d, 1H, C_8-H, J=8.85 Hz), 7.76 (d, br, 1H, C_4-H, J=7.24 Hz), 8.18 (d, br, 1H, C_2-H, J=4.42 Hz), 9.94 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{11}N_3O_4$: found (calc) C-58.64 (58.94), H-3.84 (3.85), N-14.77 (14.73).

8.12. 7-Acetamido-6-amino-5H-[1]benzopyrano[2,3-b]pyridine (93):

7-Acetamido-6-nitro-1-azaxanthene (0.5 g, 1.75 mmol) was added to 100 ml of 95% ethanol. Palladium-charcoal (100 mg, 10%) catalyst and 0.22 ml (6.9 mmol) of hydrazine hydrate were added and the reaction mixture refluxed for 1.5 hr. The reaction was followed by TLC and a light green solution formed, indicated the completion of the reaction. The hot reaction mixture was filtered through Celite, the filtrate was evaporated *in vacuo* and the residue recrystallized from methanol to give 7-acetamido-6-amino-1-azaxanthene (0.29 g, 65%). Mp 250^0C ; ir (KBr) (cm^{-1}): 3426, 3336 (NH_2), 3221 (NH), 1647 (NHC=O) ; ^1H nmr (DMSO-d_6) δ: 2.12 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.65 (s, br, 2H, NH_2, exch.), 6.38 (d, 1H, C_9-H, J=8.07 Hz), 7.06 (m, 2H, C_3-H, C_8-H), 7.64 (d, br, 1H, C_4-H, J=7.49 Hz), 8.12 (d, br, 1H, C_2-H, J=4.61 Hz), 9.12 (s, 1H, NH,

exch.) ; microanalysis for $C_{14}H_{13}N_3O_2$: found (calc) C-65.32 (65.88), H-5.27 (5.09), N-16.30 (16.47) ; high resolution mass spectrum: found 255.1000, calculated 255.1007.

8.13. 2-Methylpyrido[3',2':5,6]pyrano[3,2-e](1H,11H)-benzimidazole (94):

A solution of 7-acetamido-6-amino-1-azaxanthene (0.5 g, 1.6 mmol) in conc. HCl-ethanol (2 : 1, 25 ml) was refluxed for 8 hr. After cooling the reaction mixture, ethanol was removed *in vacuo* and basified with aqueous ammonia. The mixture was extracted with ethyl acetate (3x20 ml), dried (Na_2SO_4) and concentrated. The residue was takenup in acetone (5 ml) and the insoluble portion filtered and recrystallized from acetonitrile to give the benzimidazole (94) (0.30 g, 65%). Mp 298^{0}C ; ir (KBr) (cm^{-1}): 3418 (NH), 1630 (C=N) ; ^{1}H nmr (DMSO-d_6) δ: 2.55 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 6.94 (d, 1H, C_5-H, J=8.56 Hz), 7.14 (dd, 1H, C_9-H, J=7.3, 4.66 Hz), 7.32 (d, 1H, C_4-H, J=8.56 Hz), 7.78 (d, br, 1H, C_{10}-H, J=7.3 Hz), 8.15 (d, br, C_8-H, J=4.66 Hz), 12.1 (s, br, NH, exch.) ; microanalysis for $C_{14}H_{11}N_3O$: found (calc) C-70.36 (70.87), H-4.67 (4.64), N-17.51 (17.72) ; high resolution mass spectrum: found 237.0889, calculated 237.0901.

8.14. 7-Acetamido-5H-[1]benzopyrano[2,3-b]pyridin-5-ol:

7-Acetamido-1-azaxanthone (73e) (1.2 g, 4.72 mmol) was added to 300 ml of methanol and stirred at room temperature. Sodium borohydride (0.8g, 21.13 mmol) was added to the reaction mixture in small quantities. The reaction was monitored by TLC. On completion of the reaction, the mixture appeared as a pale green solution. Methanol was evaporated *in vacuo* and to the resulting yellow powder was added 100 ml of cold water. The undissolved portion was filtered, washed with water and dried. Recrystallization of the product from methanol gave 7-acetamido-1-azaxanthen-5-ol (1.1 g, 91%). Mp 207^{0}C ; ir (KBr) (cm^{-1}): 3430 (br, OH, NH), 1677 (NHC=O) ; ^{1}H nmr (DMSO-d_6) δ: 2.08 (s, 3H, CH_3), 5.72 (d, 1H, C_5-H; J=7.43 Hz), 6.20 (d, 1H, C_5-OH, J=7.43 Hz), 7.10 (d, 1H, C_9-H, J=8.84 Hz), 7.22 (dd, 1H, C_3-H, J=7.68, 4.64 Hz), 7.56 (dd, 1H, C_8-H, J=8.5, 2.65 Hz), 7.88 (d, 1H, C_6-H, J=2.65 Hz), 8.02 (dd, 1H, C_4-H, J=7.68, 1.75 Hz), 8.26

(dd, 1H, C_2-H, J=4.64, 1.75 Hz), 9.92 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{12}N_2O_3$: found (calc) C-65.21 (65.61), H-4.78 (4.72), N-10.86 (10.93).

8.15. 7-Acetamido-5H-[1]benzopyrano[2,3-b]pyridine (95):

7-Acetamido-1-azaxanthen-5-ol (1.0 g, 3.9 mmol) was dissolved in 15 ml of glacial acetic acid by warming on a water bath and then stirred at 0^0C. Sodium borohydride (0.315 g, 8.33 mmol) was added cautiously in small portions and the reaction mixture was then allowed to stir for 45 min. A white precipitate formed and the mixture was poured into crushed ice (100 ml). The precipitate was filtered, dried and recrystallized from methanol to give 7-acetamido-1-azaxanthene (95) as white fluffy crystals (0.90 g, 96%). Mp 235^0C ; ir (KBr) (cm^{-1}): 3262 (NH), 1679 (NHC=O) ; ^{1}H nmr (DMSO-d_6/$CDCl_3$) δ: 2.12 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.02 (d, 1H, C_9-H, J=8.41 Hz), 7.10 (dd, 1H, C_3-H, J=7.44, 4.68 Hz), 7.38 (dd, 1H, C_8-H, J=8.41, 2.58 Hz), 7.65 (m, 2H, C_6-H, C_4-H), 8.14 (dd, 1H, C_2-H, J=4.68, 2.26 Hz), 9.70 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{12}N_2O_2$: found (calc) C-69.66 (69.98), H-5.07 (5.03), N-11.76 (11.66).

8.16. 7-Acetamido-8-nitro-5H-[1]benzopyrano[2,3-b]pyridine (96):

7-Acetamido-1-azaxanthene (95) (1.0 g, 4.1 mmol) was dissolved in 5 ml of conc. H_2SO_4 and stirred at $0\text{-}5^0$C. Potassium nitrate (0.462 g, 4.5 mmol), dissolved in 4 ml of conc. H_2SO_4 was then added dropwise. The resulting reddish brown solution was stirred for 3 hr, while maintaining the temperature at $0\text{-}5^0$C and then poured into crushed ice (150 ml). Ammonium hydroxide solution (30%) was added to the resulting solution until a yellow precipitate was formed. The precipitate was filtered, dried and recrystallized from ethanol to give 7-acetamido-8-nitro-1-azaxanthene (96) as yellow crystals (0.9 g, 75%). Mp 197^0C ; ir (KBr) (cm^{-1}): 3385 (NH), 1515, 1294 (NO_2) ; ^{1}H nmr (DMSO-d_6) δ: 2.08 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.24 (dd, 1H, C_3-H, J=7.30, 4.66 Hz), 7.54 (s, 1H, C_6-H), 7.76 (s, 1H, C_9-H), 7.82 (d, br, 1H, C_4-H, J=7.30Hz), 8.22 (dd, 1H, C_2-H,

J=4.66, 2.24 Hz), 9.20 (s, 1H, NH, exch.) ; microanalysis for $C_{14}H_{11}N_3O_4$: found (calc) C-59.17 (58.94), H-3.86 (3.88), N-14.57 (14.73).

8.17. 7-Acetamido-8-amino-5H-[1]benzopyrano[2,3-b]pyridine (97):

7-Acetamido-8-nitro-1-azaxanthene (96) (0.5 g,1.7 mmol) was added to 100 ml of 95% ethanol and palladium-charcoal catalyst (0.1g, 10%) and hydrazine hydrate (0.4 ml, 12.6 mmol) were then added. The mixture was refluxed for 1.5 hr at which time the color of the solution changed from orange to colorless. The hot reaction mixture was filtered through Celite and the Celite filter was washed twice with 20 ml portions of hot ethanol. The combined filtrate was evaporated *in vacuo* and the product recrystallized from ethanol to give 7-acetamido-8-amino-1-azaxanthene (97) (0.35 g, 76%). Mp 263^{0}C ; ir (KBr) (cm^{-1}): 3418, 3328, 3254 (NH_2, NH), 1646 (NHC=O) ; ^{1}H nmr (DMSO-d_6) δ: 2.02 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 5.0 (s, 2H, NH_2, exch.), 6.5 (s, 1H, C_9-H), 7.06 (s, 1H, C_6-H), 7.16 (dd, 1H, C_3-H, J=7.21, 4.75 Hz), 7.74 (dd, 1H, C_4-H, J=7.21, 2.28 Hz), 8.14 (dd, 1H, C_2-H, J=4.75, 2.28 Hz) ; microanalysis for $C_{14}H_{13}N_3O_2$: found (calc) C-65.62 (65.86), H-5.16 (5.13), N-16.90 (16.46) ; high resolution mass spectrum: found 255.1008, calculated 255.1007.

8.18. 7,8-Diamino-5H-[1]benzopyrano[2,3-b]pyridine (98):

7-Acetamido-8-amino-1-azaxanthene (97) (0.5 g, 1.9 mmol) was added to a mixture of 10 ml of conc. HCl and 5 ml of ethanol. The reaction mixture was refluxed for 12 hr and poured into crushed ice (50 ml) and basified with (30%) ammonium hydroxide solution. A light brown fluffy precipitate which formed was filtered, dried and recrystallized from ethanol to give 7,8-diamino-1-azaxanthene (98) (0.25 g, 60%). Mp 189^{0}C; ir (KBr) cm^{-1} : 3353 (br, NH_2), 1638 (C=C) ; ^{1}H nmr (DMSO-d_6) δ: 3.9 (s, 2H, CH_2), 4.5 (s, br, 4H, $2NH_2$, exch.), 6.34 (s, 1H, C_9-H), 6.38 (s, 1H, C_6-H), 7.04 (dd, 1H, C_3-H, J=7.45, 4.79Hz), 7.64 (d, br, 1H, C_4-H, J=7.45 Hz), 8.08 (d, br, 1H, C_2-H,

J=4.79 Hz) ; microanalysis for $C_{12}H_{11}N_3O$: found (calc) C-66.94 (67.58), H-5.13 (5.19), N-19.23 (19.70) ; high resolution mass spectrum: found 213.0896, calculated 213.0901.

8.19. 2-Methylpyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzimidazole (99):

7,8-Diamino-1-azaxanthene (98) (0.35 g, 1.6 mmol) was dissolved in 5 ml of glacial acetic acid and the resulting solution was refluxed for 5-6 hr. This was then cooled, and basified with 30% ammonium hydroxide solution and the resulting fluffy precipitate was filtered and recrystallized from ethanol : water (3 : 2) to give benzimidazole (99) (0.3 g, 78%). Mp 305^{0}C ; ir (KBr) (cm^{-1}): 3133 (NH), 2918 (C-H), 1581 (C=C) ; ^{1}H nmr (DMSO-d_6) δ: 2.46 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.16 (dd, 1H, C_8-H, J=7.37, 4.33 Hz), 7.24 (s, 1H, C_4-H), 7.38 (s, 1H, C_{11}-H), 7.76 (d, br, 1H, C_9-H, J=7.37 Hz), 8.18 (d, br, 1H, C_7-H, J=4.33 Hz) ; microanalysis for $C_{14}H_{11}N_3O$: found (calc) C-70.44 (70.86), H-4.55 (4.67), N-17.91 (17.71) ; high resolution mass spectrum: found 237.0895, calculated 237.0901.

8.20. Pyrido[3',2':5,6]pyrano[3,2-e]benzotriazol-11(1H,11H)-one (100):

7-Acetamido-6-amino-1-azaxanthone (89) (0.4 g, 1.48 mmol) was dissolved in 8 ml of conc. HCl and stirred at -5^{0}C. Sodium nitrite (0.2 g, 2.97 mmol), dissolved in 2 ml of water, was added dropwise so that the temperature of the reaction mixture did not rise above 0^{0}C. The reaction was then stirred for 1 hr and the white precipitate which formed was filtered, washed free of acid with water, and dried. Recrystallization from DMF gave benzotriazole (100) (0.30 g, 85%). Mp 255^{0}C ; ir (KBr) (cm^{-1}): 3500 (NH), 1635 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 7.76 (m, 2H, C_5-H, C_9-H), 8.62 (d, 1H, C_4-H, J=10.02 Hz), 8.80 (dd, 1H, C_{10}-H, J=7.51, 1.78 Hz), 8.94 (dd, 1H, C_8-H, J=4.51, 1.78 Hz), 9.90 (s, br, NH, exch.) ; microanalysis for $C_{12}H_6N_4O_2$: found (calc) C-60.16 (60.5), H-2.61 (2.61), N-23.53 (23.52).

8.21. Pyrido[3',2':5,6]pyrano[3,2-e](1H,11H)benzotriazole (101):

7-Acetamido-6-amino-1-azaxanthene (93) (0.07 g, 0.27 mmol) was dissolved in 3 ml of conc. HCl and stirred at -5^{0}C. Sodium nitrite (0.05 g, 0.72 mmol), dissolved in 2 ml of water, was added slowly from an addition funnel, so that the temperature of the reaction mixture did not rise above 0^{0}C. The mixture was stirred for 1 hr, poured into crushed ice (20 ml), and basified with 30% ammonium hydroxide. The pink-colored fluffy precipitate which formed was filtered, dried and recrystallized from methanol to give benzotriazole (101) (0.04 g, 71%). Mp 280^{0}C ; ir (KBr) (cm^{-1}): 3405 (NH), 1580 (C=C) ; ^{1}H nmr (DMSO-d_6) δ: 4.46(s, 2H, CH_2), 7.26 (m, 2H, C_5-H, C_9-H), 7.84 (d, 1H, C_4-H, J=8.84 Hz), 7.90 (dd, 1H, C_{10}-H, J=7.32, 2.20 Hz), 8.22 (dd, 1H, C_8-H, J=4.72, 2.20 Hz) ; high resolution mass spectrum calculated for $C_{12}H_8N_4O$: found 224.0694, calculated 224.0698.

8.22. Pyrido[3',2':5,6]pyrano[3,2-f](1H,10H)benzotriazole (102):

7-Acetamido-8-amino-1-azaxanthene (97) (0.1 g, 0.392 mmol) was dissolved in 5 ml of conc. HCl and stirred at -5^{0}C. Sodium nitrite (0.14 g, 2.0 mmol) was dissolved in 1.5 ml of water and added dropwise to the HCl solution. This was stirred for a further 1 hr and poured into crushed ice (50 ml), and basified with 30% ammonium hydroxide solution. The creamy white precipitate which formed was filtered, dried and recrystallized from methanol to give benzotriazole (102) (0.64 g, 73%). Mp >340^{0}C ; ir (KBr) (cm^{-1}): 3460 (NH) ; ^{1}H nmr (DMSO-d_6) δ: 4.32 (s, 2H, CH_2), 7.22 (dd, 1H, C_8-H, J=7.25, 4.06 Hz), 7.66 (s, 1H, C_4-H), 7.84 (dd, 1H, C_9-H, J=7.25, 2.32 Hz), 7.92 (s, 1H, C_{11}-H), 8.20 (d br, 1H, C_7-H, J=4.0 Hz) ; microanalysis for $C_{12}H_8N_4O$: found (calc) C-63.84 (64.27), H-3.78 (3.59), N-25.40 (24.99) ; high resolution mass spectrum: found 224.0702, calculated 224.0698.

8.23. 2-Aminopyrido[3',2':5,6]pyrano[2,3-g]benzothiazol-11(11H)-one (103):

7-Amino-1-azaxanthone (73c) (1.0 g, 4.71 mmol) was dissolved in 25 ml of glacial acetic acid. Ammonium thiocyanate (0.71 g, 9.43 mmol) was added and the reaction stirred at 0-5^{0}C. Bromine (0.48 ml, 9.43 mmol), dissolved in 20 ml of glacial acetic acid, was added dropwise at such a rate as to keep the temperature below 10^{0}C. Stirring was continued for an additional 0.5 hr. Benzothiazole (103) which precipitated as its hydrobromide salt, was collected by filtration. This was then dissolved in hot water and basified with a saturated solution of sodium carbonate. The resulting precipitate was filtered, washed with water and dried. Recrystallization from glacial acetic acid gave benzothiazole (103) (1.1 g, 87%) ; mp 315^{0}C ; ir (KBr) (cm^{-1}): 3443, 3304 (NH_2), 1646 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 7.68 (m, 4H, C_9-H, C_5-H, NH_2), 7.92 (d, 1H, C_4-H, J=8.94 Hz), 8.68 (d, br, 1H, C_{10}-H, J=7.56 Hz), 8.84 (d, br, 1H, C_8-H, J=3.44 Hz) ; microanalysis for $C_{13}H_7N_3O_2S$: found (calc) C-57.73 (57.99), H-2.62 (2.60), N-15.36 (15.61).

8.24. 7-Amino-5H-[1]benzopyrano[2,3-b]pyridine (104):

To 7-acetamido-1-azaxanthene (95) (1.0 g, 4.1 mmol) was added 10 ml of conc. HCl and 5 ml of methanol. The mixture was refluxed for 3 hr, poured into crushed ice (100 ml) and basified with 30% ammonium hydroxide solution. The light yellow precipitate which formed was filtered, dried and recrystallized from benzene to give 7-amino-1-azaxanthene (104) (0.65 g, 78%). Mp 135^{0}C ; ir (KBr) (cm^{-1}): 3427, 3344 (NH_2), 1622 (C=N) ; ^{1}H nmr ($CDCl_3$) δ: 4.04 (s, 2H, CH_2), 6.50 (d, 1H, C_6-H, J=3.8 Hz), 6.58 (dd, 1H, C_8-H, J=12.24, 3.80 Hz), 7.00 (m, 2H, C_3-H, C_9-H), 7.52 (d, br, 1H, C_4-H, J=7.34 Hz), 8.18 (d, br, 1H, C_2-H, J=4.08 Hz) ; microanalysis for $C_{12}H_{10}N_2O$: found (calc) C-72.45 (72.70), H-5.12 (5.08), N-13.77 (14.13).

8.25. 2-Aminopyrido[3',2':5,6]pyrano[2,3-g](11H)benzothiazole (105):

7-Amino-1-azaxanthene (104) (0.75 g, 3.7 mmol) and 0.57 g (7.4 mmol) of ammonium thiocyanate were dissolved in 25 ml of glacial acetic acid and stirred at 0-5^{0}C. Bromine (0.38 ml, 7.4 mmol) dissolved in 10 ml of glacial acetic acid, was added dropwise so that the temperature of the reaction mixture did not rise above 10^{0}C. The mixture was stirred for 1 hr and the orange-yellow precipitate (hydrobromide salt of benzothiazole) was filtered, dissolved in hot water and basified with saturated sodium carbonate solution. The precipitate of free amine which formed was filtered, washed with excess water, dried and recrystallized from acetonitrile to give benzothiazole (105) (0.48 g, 50%). Mp 289^{0}C ; ir (KBr) (cm^{-1}): 3287, 3123 (NH_2), 1638 (C=N) ; ^{1}H nmr (DMSO-d_6) δ: 4.16 (s, 2H, CH_2), 7.08 (d, 1H, C_5-H, J=8.44 Hz), 7.22 (dd, 1H, C_9-H, J=7.19, 4.21 Hz), 7.30 (d, 1H, C_4-H, J=8.44 Hz), 7.56 (s, br, 2H, NH_2), 7.86 (d, br, 1H, C_{10}-H, J=7.19 Hz), 8.22 (d, br, 1H, C_8-H, J=4.21 Hz) ; microanalysis for $C_{13}H_9N_3SO$: found (calc) C-60.15 (61.15), H-3.41 (3.55), N-16.33 (16.46) ; high resolution mass spectrum: found 255.0452, calculated 255.0466.

8.26. General procedure for the synthesis of pyrido[3',2':5,6]pyrano[3,2-c]indol-11(3H, 11H)-ones (108 a-f) :

A solution of 0.31 g (1.46 mmol) of 7-amino-1-azaxanthone (73c) in 8 ml of conc. HCl was stirred at -5 to 0^{0}C. A solution of sodium nitrite (0.14 g, 2.0 mmol) in 2 ml of water, was added dropwise so that the temperature of the reaction mixture did not rise above 0^{0}C. Stirring was continued for 30 min when an orange colored solution of the diazonium salt (106) was formed. A solution of stannous chloride (0.7 g, 3.6 mmol), in 2 ml of conc. HCl was added dropwise to give the HCl salt of 7-hydrazino-1-azaxanthone (107) as a yellow precipitate. Stirring was continued for a further 1.5 hr. Ethanol (95%, 6 ml) and 0.13 ml (1.80 mmol) of propionaldehyde were added and the reaction mixture refluxed for 1 hr. The mixture was allowed to cool to room temperature and the precipitate

which formed was filtered, washed with water and dried. Recrystallization (activated charcoal) of the product from methanol gave indole (108 a) (0.30 g, 82%). Mp246^{0}C ; ir (KBr) (cm^{-1}): 3189 (NH), 1655 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 2.72 (s, 3H, CH_3), 7.36 (d, 1H, C_5-H, J=8.53 Hz), 7.42 (s, br, 1H, C_2-H), 7.58 (dd, 1H, C_9-H, J=7.89, 4.58 Hz), 7.90 (d, 1H, C_4-H, J=8.53 Hz), 8.66 (dd, 1H, C_{10}-H, J=7.89, 2.02 Hz), 8.78 (dd, 1H, C_8-H, J=4.58, 2.02 Hz), 11.51 (s, 1H, NH, exch.) ; microanalysis for $C_{15}H_{10}N_2O_2$: found (calc) C-71.67 (72.27), H-3.96 (3.63), N-11.18 (11.16) ; high resolution mass spectrum: found 250.0740 calculated 250.0742.

8.26.1. 1-n-Butyl-2-methylpyrido[3',2':5,6]pyrano[3,2-e]indol-11(3H,11H)-one (108 b):

Yield 83% ; mp 250^{0}C (methanol) ; ir (KBr) (cm^{-1}): 3215 (NH), 1650 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 0.88 (t, 3H, $CH_2CH_2CH_2\underline{CH_3}$, J=6.83 Hz), 1.40 (m, 4H, $CH_2\underline{CH_2CH_2}CH_3$), 2.45 (s, 3H, 2-$CH_3$), 3.21 (t, 2H, $\underline{CH_2}CH_2CH_2CH_3$, J=6.07 Hz), 7.34 (d, 1H, C_5-H, J=8.78 Hz), 7.62 (dd, 1H, C_9-H, J=7.76, 4.49 Hz), 7.85 (d, 1H, C_4-H, J=8.78 Hz), 8.70 (dd, 1H, C_{10}-H, J=7.76, 2.04 Hz), 8.82 (dd, 1H, C_8-H, J=4.49, 2.04 Hz), 11.60 (s, 1H, NH, exch.) ; microanalysis for $C_{19}H_{18}N_2O_2$: found (calc) C-74.35 (74.48), H-5.85 (5.92), N-9.13 (9.14).

8.26.2. 2-Methyl-1-n-pentylpyrido[3',2':5,6]pyrano[3,2-e]indol-11(3H,11H)-one(108 c):

Yield 80% ; mp 232^{0}C (methanol) ; ir (KBr) (cm^{-1}): 3250 (NH), 1650 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 0.86 (t, br, 3H, $(CH_2)_4\underline{CH_3}$), 1.32 (m, 4H, $CH_2CH_2\underline{CH_2CH_2}CH_3$), 1.46 (m, 2H, $CH_2\underline{CH_2}(CH_2)_2CH_3$) 2.42 (s, 3H, 2-$CH_3$), 3.2 (t, 2H, $\underline{CH_2}(CH_2)_3CH_3$, J=6.89 Hz), 7.30 (d, 1H, C_5-H, J=9.08 Hz), 7.60 (dd, 1H, C_9-H, J=7.64, 4.42 Hz), 7.84 (d, 1H, C_4-H, J=9.08 Hz), 8.70 (dd, 1H, C_{10}-H, J=7.64, 1.79 Hz), 8.80 (dd, 1H, C_8-H, J=4.42, 1.79 Hz), 11.6 (s, 1H, NH, exch.) ; microanalysis for $C_{20}H_{20}N_2O_2$: found (calc) C-74.77 (74.97), H-6.26 (6.29), N-8.74 (8.74).

8.26.3. 1-Phenylpyrido[3',2':5,6]pyrano[3,2-c]indol-11(3H,11H)-one (108 d)

Yield 70% ; mp 292^{0}C (acetonitrile) ; ir (KBr) (cm^{-1}): 3240 (NH), 1650 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 7.28 (m, 5H, 1-Ph), 7.55 (m, 2H, C_5-H, C9-H), 7.74 (d, 1H, C_2-H, J=3.2 Hz), 8.06 (d, 1H, C_4-H, J=8.69 Hz), 8.48 (dd, 1H, C_{10}-H, J=7.09, 2.28 Hz), 8.78 (dd, 1H, C_8-H, J=4.34, 2.28 Hz), 11.55 (s, 1H, NH, exch.) ; microanalysis for $C_{20}H_{12}N_2O_2$: found (calc) C-73.42 (76.9), H-3.64 (3.87), N-8.67 (8.97) ; high resolution mass spectrum: found 312.0900, calculated 312.0898.

8.26.4. Pyrido[3',2':5,6]pyrano[3,2-i]-1,2,3,4-tetrahydrocarbazol-13(5H,13H)-one (108 e):

Yield 72% ; mp 285^{0}C (methanol) ; ir (KBr) (cm^{-1}): 3240 (NH), 1655 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 1.84 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.84 (m, 2H, 4-CH_2), 3.32 (m, 2H, 1-CH_2), 7.3 (d, 1H, C_7-H, J=8.77 Hz), 7.6 (dd, 1H, C_{11}-H, J=7.67, 5.15 Hz), 7.82 (d, 1H, C_6-H, J=8.77 Hz), 8.66 (dd, 1H, C_{12}-H, J=7.67, 1.97 Hz), 8.82 (dd, 1H, C_{10}-H, J=5.15, 1.97 Hz), 11.60 (s, 1H, NH, exch.) ; microanalysis for $C_{18}H_{14}N_2O_2$: found (calc) C-74.04 (74.46), H-4.87 (4.86), N-9.64 (9.64) ; high resolution mass spectrum: found 290.1054, calculated 290.1055.

8.26.5. Pyrido[3',2':5,6]pyrano[3,2-h]cyclopentano[1,2-b]indol-12(4H,12H)-one (108 f):

Yield 71% ; mp 310^{0}C (acetonitrile) ; ir (KBr) (cm^{-1}): 3410 (NH), 1650 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 2.42 (q, 2H, 2-CH_2, J=6.88 Hz), 2.78 (t, 2H, 3-CH_2, J=7.37 Hz), 3.26 (t, 2H, 1-CH_2, J=7.54 Hz), 7.24 (d, 1H, C_6-H, J=8.75 Hz), 7.58 (dd, 1H, C_{10}-H, J=7.41, 4.74 Hz), 8.75 (d, 1H, C_5-H, J=8.75 Hz), 8.64 (dd, 1H, C_{11}-H, J=7.41, 2.67 Hz), 8.78 (dd, C_9-H, J=4.74, 2.67 Hz), 11.6 (s, 1H, NH, exch.) ; microanalysis for $C_{17}H_{12}N_2O_2$: found (calc) C-72.84 (73.89), H-4.38 (4.37), N-10.15 (10.14) ; high resolution mass spectrum: found 276.0896, calculated 276.0898.

8.27. 7-Hydroxy-5H-[1]benzopyrano[2,3-b]pyridin-5-one (109):

7-Methoxy-1-azaxanthone (73d) (1 g, 4.4 mmol) was placed in 10 ml of 48% hydrobromic acid. The mixture was refluxed for 6 hr, resulting in the formation of a green precipitate. The reaction mixture was poured into crushed ice (100 ml) and the precipitate which formed was filtered and recrystallized from ethanol to afford 7-hydroxy-1-azaxanthone (109) (0.85 g, 90%). Mp 279^{0}C ; ir (KBr) (cm^{-1}): 3330 (OH), 1663 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 7.36 (dd, 1H, C_8-H, J=8.69, 2.91 Hz), 7.50 (m, 2H, C_3-H, C_9-H), 7.60 (d, 1H, C_6-H, J=2.91 Hz), 8.68 (dd, 1H, C_4-H, J=7.80, 1.92 Hz), 8.76 (dd, 1H, C_2-H, J=4.78, 1.92 Hz), 9.70 (s, br, 1H, OH, exch.) ; microanalysis for: $C_{12}H_7NO_3$: found (calc) C-67.49 (67.60), H-3.45 (3.30), N-6.35 (6.57).

8.28. 7-O-Allyl-5H-[1]-benzopyrano[2,3-b]pyridin-5-one (110):

7-Hydroxy-1-azaxanthone (109) (1.0 g, 4.6 mmol) and 2.6 g (18.8 mmol) of dry potassium carbonate were placed in 150 ml of dry acetonitrile. The mixture was refluxed for 15 min to give an orange-colored precipitate of phenolate salt. Allylbromide (0.5 ml, 5.7 mmol) was added and the reaction mixture refluxed for 12 hr. The hot reaction mixture was filtered through Celite which was then washed twice with 25 ml portions of chloroform. The combined filtrate was evaporated *in vacuo* and the residue recrystallized from acetone to give 7-O-allyl-1-azaxanthone (110) (1.2 g, 98%). Mp 122^{0}C ; ir (KBr) (cm^{-1}): 2926 (C-H), 1658 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 4.66 (m, 2H, OCH_2), 5.36 (dd, 1H, OCH_2-CH=$\underline{CH_2}$, J_{cis}=10.64 Hz, J_{gem}=1.73 Hz), 5.50 (dd, 1H, OCH_2-CH=$\underline{CH_2}$, J_{trans}=17.19 Hz, J_{gem}=1.73 Hz), 6.10 (m, 1H, OCH_2-$\underline{CH}$=CH_2), 7.44 (m, 2H, C_3-H, C_9-H), 7.60 (d, 1H, C_8-H, J=9.0 Hz), 7.7 (d, 1H, C_6-H, J=3.27 Hz), 8.75 (m, 2H, C_2-H, C_4-H): microanalysis for $C_{15}H_{11}NO_3$: found (calc) C-71.22 (71.13), H-4.45 (4.37), N-5.48 (5.53).

8.29. 7-Hydroxy-6-allyl-5H-[1]benzopyrano[2,3-b]pyridin-5-one (111):

7-O-Allyl-1-azaxanthone (110) (0.5 g, 1.9 mmol) was dissolved in 5 ml of N,N-dimethylaniline and refluxed for 3 hr and then poured into a mixture of 25 ml of 2N HCl and 15 ml of crushed ice. The yellow precipitate which formed was filtered, dissolved in 35 ml of 10% sodium hydroxide solution, and washed with 50 ml of chloroform to remove impurities and any unreacted material. Acidification with HCl gave a bright yellow precipitate which was recrystallized from acetone to give 7-hydroxy-6-allyl-1-azaxanthone (111) (0.40 g, 80%). Mp 199^{0}C ; ir (KBr) (cm^{-1}): 3156 (OH), 1655 (C=O) ; ^{1}H nmr ($CDCl_3$/DMSO-d_6) δ: 4.24 (m, 2H, $\underline{CH_2}$-CH=CH_2), 5.02 (m, 2H, CH_2-CH=$\underline{CH_2}$), 6.16 (m, 1H, CH_2-$\underline{CH}$=CH_2), 7.4 (m, 3H, C_3-H, C_8-H, C_9-H), 8.7 (m, 2H, C_2-H, C_4-H), 9.04 (s, 1H, OH, exch.) ; microanalysis for: $C_{15}H_{11}NO_3$: found (calc) C-70.93 (71.13), H-4.48 (4.37), N-5.63 (5.53).

8.30. 2-Methylpyrido[3',2':5,6]pyrano[3,2-e]-1,2-dihydrobenzofuran-11(11H)-one (112):

7-Hydroxy-6-allyl-1-azaxanthone (111) (0.35 g, 1.3 mmol) was dissolved in a mixture of 8 ml of 48% hydrobromic acid and 2 ml of glacial acetic acid. The solution was refluxed for 1 hr and poured into crushed ice (50 ml). A greenish-yellow solid which separated was filtered and recrystallized from methanol to give dihydrobenzofuran (112) (0.25 g, 71%). Mp 172^{0}C ; ir (KBr) (cm^{-1}): 2975 (C-H), 1655 (C=O) ; ^{1}H nmr ($CDCl_3$) δ: 1.54 (d, 3H, CH_3, J=6.5 Hz), 3.42 (dd, 1H, C_1-H, J_{gem}=17.83 Hz, J_{vic}=8.27 Hz), 3.98 (dd, 1H, C_1-H, J_{gem}=17.83 Hz, J_{vic}=9.05 Hz), 5.14 (m, 1H, C_2-H), 7.20 (d, 1H, C_5-H, J=8.83 Hz), 7.44 (m, 2H, C_9-H, C_4-H), 8.68 (dd, 1H, C_{10}-H, J=7.51, 2.30 Hz), 8.74 (dd, 1H, C_8-H, J=4.41, 2.30 Hz) ; microanalysis for $C_{15}H_{11}NO_3$: found (calc) C-70.74 (71.13), H-4.41 (4.37), N-5.41 (5.53).

8.31. 2-Methylpyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11(11H)-one (113):

A mixture of dihydrobenzofuran (112) (0.63 g, 2.4 mmol), N-bromosuccinimide (0.531 g, 29.8 mmol) and benzoylperoxide (0.03 g, 0.123 mmol) were added to 30 ml of carbon tetrachloride. The mixture was refluxed for 3 hr during which time the initial deep brown solution evolved reddish-brown fumes. Continued refluxing resulted in the precipitation of a solid which was recrystallized from acetone to give benzofuran (113) (0.50 g, 80%). Mp 200^{0}C ; ir (KBr) (cm^{-1}): 3082 (Ar,C=C), 1655 (C=O) ; ^{1}H nmr ($CDCl_3$) δ: 2.60 (s, 3H, CH_3), 7.48 (m, 3H, C_9-H, C_5-H, C_1-H), 7.82 (d, 1H, C_4-H, J=8.91 Hz), 8.78 (m, 2H, C_8-H, C_{10}-H) ; microanalysis for $C_{15}H_9NO_3$: found (calc) C-70.08 (71.7), H-3.81 (3.61), N-5.30 (5.57) ; high resolution mass spectra: found 251.0568, calculated 251.0582

8.32. 2-Methylpyrido[3',2':5,6]pyrano[3,2-e](11H)-1,2-dihydrobenzofuran (114):

Dihydrobenzofuran (112) (0.46 g, 1.8 mmol) was dissolved in 50 ml of methanol and stirred at room temperature. Sodium borohydride (0.2 g, 5.2 mmol) was added portionwise to the reaction mixture with continuous stirring. After 0.5 hr, methanol was evaporated *in vacuo* and the residue was extracted with chloroform and the chloroform solution washed twice with 50 ml portions of water. Evaporation of chloroform *in vacuo* left an oily residue which was dissolved in 5 ml of glacial acetic acid and stirred at 0^{0}C. Sodium borohydride (0.2 g, 5.4 mmol) was added cautiously to the acetic acid solution and stirred for 1 hr. The reaction mixture was poured into crushed ice (50 ml) and set aside overnight. Light yellow crystals which formed were filtered and dried to give dihydrobenzofuran (114) (0.35 g, 80%). Mp 112^{0}C ; ir (KBr) (cm^{-1}): 2984 (C-H), 1581 (C=C) ; ^{1}H nmr ($CDCl_3$) δ: 1.50 (d, 3H, CH_3, J=6.45 Hz), 2.72 (dd, 1H, C_1-H, J_{gem}=15.31 Hz,J_{vic}=7.65 Hz), 3.22 (dd, 1H, C_1-H, J_{gem}=15.31 Hz, J_{vic}=8.93 Hz), 3.92 (s, 2H, 11-CH_2), 4.86 (m, 1H, C_2-H), 6.60 (d, 1H, C_5-H or C_4-H, J=8.63 Hz), 6.90 (d, 1H, C_4-H or C_5-H, J=8.63 Hz), 7.00 (dd, 1H, C_9-H, J=7.19, 4.55 Hz), 7.5 (dd, 1H,

C_{10}-H, J=7.19, 2.15 Hz), 8.14 (dd, 1H, C_8-H, J=4.55, 2.15 Hz) ; microanalysis for $C_{15}H_{13}NO_2$: found (calc) C-74.33 (75.29), H-5.41 (5.47), N-5.64 (5.85) ; high resolution mass spectrum: found 239.0934, calculated 239.0946.

8.33. 2-Aminopyrido[3',2':5,6]pyrano[3,2-e]benzofuran-11(11H)-one (116):

7-Hydroxy-1-azaxanthone (109) (1.0 g, 4.6 mmol) was dissolved in a mixture of 15 ml of conc. HCl and 8 ml of conc. H_2SO_4 and stirred on an oil bath at 70-75^{0}C. Paraformaldehyde (1.4 g) was added and a gentle stream of HCl gas was passed into the reaction mixture. A greenish yellow precipitate was formed in about 1 hr. The reaction mixture was poured into crushed ice and the precipitate which was filtered and dried (1.0 g, 80%).

The precipitate obtained above (0.5 g) was added to 35 ml of dioxane. Potassium cyanide (0.4 g, 6.1 mmol) dissolved in 10 ml of water, was added and the solution refluxed overnight to give a dark brown precipitate. The dioxane was removed *in vacuo* and the residue was treated with 20 ml of 5% sodium hydroxide to dissolve any unreacted phenol. The undissolved portion was filtered, washed with water and recrystallized from acetonitrile to give benzofuran (116) (0.4 g, 83%). Mp 240^{0}C ; ir (KBr) (cm^{-1}): 3468, 3361 (NH_2), 1646 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 6.32 (s, 1H, C_1-H), 7.05 (d, 1H, C_5-H, J=7.99 Hz), 7.20 (s, br, 2H, NH_2), 7.62 (dd, 1H, C_9-H, J=7.74, 4.49 Hz), 7.72 (d, 1H, C_4-H, J=7.99 Hz), 8.66 (dd, 1H, C_{10}-H, J=7.74, 2.00 Hz), 8.82 (dd, 1H, C_8-H, J=4.49, 2.00 Hz) ; microanalysis for $C_{14}H_8N_2O_3$: found (calc) C-66.49 (66.66), H-3.25 (3.19), N-11.69 (11.13) ; high resolution mass spectrum: found 252.0544, calculated 252.0534.

8.34. 7-Methoxy-6-nitro-5H-[1]benzopyrano[2,3-b]pyridin-5-one (117):

7-Methoxy-1-azaxanthone (73d) (1.21 g, 5.3 mmol) was dissolved in 8 ml of conc. H_2SO_4 and stirred at 0-5^{0}C and a solution of 0.7 g (6.9 mmol) of potassium nitrate, dissolved in 4 ml of conc. H_2SO_4 was added. The reaction mixture was slowly allowed to

reach room temperature and stirring continued for an additional 3 hr. The reaction mixture was poured into crushed ice (150 ml), neutralized (30% ammonium hydroxide solution) and the precipitate which formed was filtered, washed with water, dried, and recrystallized from THF to give 7-methoxy-6-nitro-1-azaxanthone (117) (1.38 g, 94.3%). Mp 268^{0}C ; ir (KBr) (cm^{-1}): 1665 (C=O), 1560, 1320 (NO_2) ; ^{1}H nmr (DMSO-d_6) δ: 4.02 (s, 3H, OCH_3), 7.66 (dd, 1H, C_3-H, J=7.88, 4.62 Hz), 8.02 (d, 1H, C_8-H, J=9.6 Hz), 8.08 (d, 1H, C_9-H, J=9.6 Hz), 8.60 (dd, 1H, C_4-H, J=7.88, 2.40 Hz), 8.90 (dd, 1H, C_2-H, J=4.62, 2.40 Hz) ; microanalysis for $C_{13}H_8N_2O_5$: found (calc) C-57.12 (57.35), H-2.85 (2.96), N-10.45 (10.29).

8.35. 7-Hydroxy-6-nitro-5H-[1]benzopyrano[2,3-b]pyridin-5-one (118):

7-Methoxy-6-nitro-1-azaxanthone (117) (1.5 g, 5.5 mmol) was mixed with 15 ml of 48% HBr and refluxed overnight during which time a precipitate formed. The reaction mixture was poured into crushed ice (100 ml) and the precipitate filtered, washed with water and dried. Recrystallization of the precipitate from ethanol, gave 7-hydroxy-6-nitro-1-azaxanthone (118) (1.12 g, 79%). Mp 254^{0}C ; ir (KBr) (cm^{-1}): 3500 (br, OH), 1665 (C=O), 1545, 1335 (NO_2) ; ^{1}H nmr (DMSO-d_6) δ: 7.66 (m, 2H, C_3-H, C_8-H), 7.90 (d, 1H, C_9-H, J=9.23 Hz), 8.60 (dd, 1H, C_4-H, J=7.24, 1.99 Hz), 8.86 (dd, 1H, C_2-H, J=4.7, 1.99 Hz), 11.5 (s, 1H, C_6-OH, exch.) ; microanalysis for $C_{12}H_6N_2O_5$: found (calc) C-55.40 (55.81), H-2.22 (2.34), N-10.89 (10.85).

8.36. 6-Amino-7-hydroxy-5H-[1]benzopyrano[2,3-b]pyridin-5-one (119):

7-Hydroxy-6-nitro-1-azaxanthone (118) (0.7 g, 2.71 mmol) was added to 100 ml of 95% ethanol and palladium-charcoal (0.1 g, 10%) and hydrazine hydrate (0.35 ml, 11.0 mmol) were then added. The mixture was refluxed for 3 hr to give a dark red solution which was filtered through Celite while hot. The filter cake was washed with 25 ml of hot ethanol and the combined filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from methanol afforded 6-amino-7-hydroxy-1-azaxanthone (119) as red

crystals (0.50 g, 82%). Mp 263^{0}C ; ir (KBr) (cm^{-1}): 3470, 3325 (br, NH_2, OH), 1650 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 6.62 (d, 1H, C_8-H, J=8.31 Hz), 7.16 (d, 1H, C_9-H, J=8.31 Hz), 7.28 (s, br, 2H, NH_2, exch.), 7.56 (dd, 1H, C_3-H, J=7.42, 4.45 Hz), 8.60 (dd, 1H, C_4-H, J=7.42, 2.52 Hz), 8.75 (dd, 1H, C_2-H, J=4.45, 2.52 Hz), 9.76 (s, 1H, OH, exch.) ; microanalysis for $C_{12}H_8N_2O_3$: found (calc) C-62.35 (63.15), H-3.51 (3.53), N-12.22 (12.27) ; high resolution mass spectrum: found 228.0535, calculated 228.0534.

8.37. Pyrido[3',2':5,6]pyrano[3,2-e]benzoxadiazol-11(11H)-one (120):

6-Amino-7-hydroxy-1-azaxanthone (119) (0.45 g, 1.97 mmol) was placed in 8 ml of conc. HCl and stirred at -5 to 0^{0}C. Sodium nitrite (0.27 g, 3.9 mmol), dissolved in 2 ml of water, was added dropwise at such a rate that the temperature of the reaction mixture did not rise above 0^{0}C. Stirring was continued for 1 hr and the precipitate which formed was filtered, washed with water and dried. Recrystallization from acetonitrile gave 0.40 g (78%) of benzoxadiazole (120). Mp 215^{0}C ; ir (KBr) (cm^{-1}): 2125 (N=N), 1670 (C=O), 1600 (C=C) ; ^{1}H nmr δ: 7.18 (d, 1H, C_5-H, J=9.84 Hz), 7.72 (dd, 1H, C_9-H, J=8.02, 4.66 Hz), 7.92 (d, 1H, C_4-H, J=9.84 Hz), 8.76 (dd, 1H, C_{10}-H, J=8.02, 2.59 Hz), 8.90 (dd, 1H, C_8-H, J=4.66, 2.59 Hz) ; high resolution mass spectrum for $C_{12}H_5N_3O_3$: found 239.0326, calculated 239.0330.

8.38. 2-Mercaptopyrido[3',2':5,6]pyrano[3,2-e]benzoxazol-11(11H)-one (121):

A mixture of 6-amino-7-hydroxy-1-azaxanthone (119) (3.0 g, 1.3 mmol), potassium ethyl xanthate (0.23 g, 1.4 mmol), 10 ml of 95% ethanol and 2 ml of water was refluxed for 5 hr. The precipitate was filtered, washed with water, dried and recrystallized from acetic acid to give (0.12 g, 35%) of benzoxazole (121). Mp >335^{0}C ; ir (KBr) (cm^{-1}): 2360 (SH), 1655 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 7.56 (d, 1H, C_5-H, J=8.73 Hz), 7.64 (dd, 1H, C_9-H, J=7.71, 4.86 Hz), 8.00 (d, 1H, C_4-H, J=8.73 Hz), 8.65 (dd, 1H, C_{10}-H, J=7.71, 1.7 Hz), 8.84 (d, br, 1H, C_8-H, J=4.86 Hz) ; microanalysis for

$C_{13}H_6N_2O_3S$: found (calc) C-57.88 (57.77), H-2.34 (2.22), N-10.13 (10.37) ; high resolution mass spectrum : calculated 270.0099, found 270.0074.

8.39. 3-Methylpyrido[3',2':5,6]pyrano[3,2-f]quinolin-12(12H)-one (123):

7-Amino-1-azaxanthone (73c) (0.45 g, 2.12 mmol) was placed in 10 ml of conc. HCl to which was added acetaldehyde (2 ml, 34.97 mmol). The mixture was refluxed for 1.5 hr and the dark brown solution which formed was poured into crushed ice (100 ml) and basified with 10% sodium hydroxide solution. The precipitate which formed was filtered, dried and recrystallized from methanol to give quinoline (123) (0.2 g, 36%) ; mp 237^0C ; ir (KBr) (cm^{-1}): 1655 (C=O), 1605 (C=N) ; ^{1}H nmr (DMSO-d_6) δ: 2.72 (s, 3H, CH_3), 7.74 (m, 2H, C_2-H, C_{10}-H), 8.10 (d, 1H, C_6-H, J=8.75 Hz), 8.42 (d, 1H, C_5-H, J=8.75 Hz), 8.78 (dd, 1H, C_{11}-H, J=7.87, 2.84 Hz), 8.94 (dd, 1H, C_9-H, J=4.81, 2.84 Hz), 10.1 (d, 1H, C_1-H, 8.75 Hz) ; microanalysis for $C_{16}H_{10}N_2O_2$: found (calc) C-73.11 (73.27), 3.98 (3.84), N-10.40 (10.68).

8.40. Pyrido[3',2':5,6]pyrano[3,2-f]1,3-benzodioxan-12(12H)-one (124):

6-Chloromethyl-7-hydroxy-1-azaxanthone (1g, 3.8 mmol) and 0.5 g of paraformaldehyde were added to 100 ml of water and heated on a water bath for 0.5 hr at 90^0C. The insoluble product was filtered and recrystallized from acetone to give benzodioxane (124) (0.70 g, 72%). Mp 190^0C ; ir (KBr) (cm^{-1}): 2910 (C-H), 1663 (C=O); ^{1}H nmr ($CDCl_3$) δ: 5.32 (s, 2H, 1-CH_2), 5.54 (s, 2H, O-CH_2-O), 7.34 (d, 1H, C_5-H, J=9.7 Hz), 7.48 (m, 2H, C_{10}-H, C_6-H), 8.64 (dd, C_{11}-H, J=6.47, 3.23 Hz), 8.78 (dd, 1H, C_9-H, J=4.85, 3.23 Hz) ; microanalysis for $C_{14}H_9NO_4$: found (calc) C-65.30 (65.87), H-3.53 (3.55), N-5.46 (5.48).

8.41. 7-Methylacetoxy-6-nitro-5H-[1]benzopyrano[2,3-b]pyridin-5-one (125):

7-Hydroxy-6-nitro-1-azaxanthone (118) (0.22 g, 0.85 mmol) was dissolved in 50 ml of acetone and sodium carbonate (0.18 g, 1.69 mmol) and methyl bromoacetate (0.12 ml, 1.26 mmol) were then added. The reaction was refluxed for 5.5 hr, by which time the reaction mixture was light pink in color. The solvent was evaporated *in vacuo* and the residue was takenup in 50 ml of chloroform and the solution filtered to remove excess sodium carbonate. The filtrate was evaporated *in vacuo* to give a pink-colored compound which was recrystallized from THF to give 7-methylacetoxy-6-nitro-1-azaxanthone (125) (0.24 g, 85%). Mp 228^{0}C ; ir (KBr) (cm^{-1}): 1755 (COOMe), 1665 (C=O), 1545, 1410 (NO_2) ; ^{1}H nmr (DMSO-d_6) δ: 3.74 (s, 3H, $COOCH_3$), 5.16 (s, 2H, OCH_2), 7.66 (dd, 1H, C_3-H, J=8.21, 5.02 Hz), 7.96 (d, 1H, C_8-H or C_9-H, J=9.58 Hz), 8.04 (d, 1H, C_9-H or C_8-H, J=9.58 Hz), 8.6 (dd, 1H, C_4-H, J=8.21, 2.28 Hz), 8.9 (dd, 1H, C_2-H, J=5.02, 2.28 Hz) ; microanalysis for $C_{15}H_{10}N_2C_7$: found (calc) C-54.34 (54.54), H-2.99 (3.05), N-8.74 (8.48).

8.42. 2-Hydroxy-2-hydrazinopyrido[3',2':5,6]pyrano[3,2-f]2,3-dihydro(1H)1,4-benzoxazin-12(12H)-one (126):

7-Methylacetoxy-6-nitro-1-azaxanthone (125) (0.25 g, 0.75 mmol) was added to 100 ml of 95% ethanol and palladium-charcoal (0.1 g, 10%) and 0.1 ml (3.0 mmol) of anhydrous hydrazine were then added. The reaction mixture was refluxed for 12 hr and gave a green precipitate which was filtered and recrystallized from acetonitrile to give dihydrobenzoxazine (126) (0.19 g,83.5%). Mp 265^{0}C ; ir (KBr) (cm^{-1}): 3480, 3350 (br, NH_2, OH), 3290 (NH), 1645 (C=O) ; ^{1}H nmr (DMSO-d_6) δ: 4.60 (s, br, 6H, OCH_2, $NHNH_2$, OH, exch. for 4H), 6.62 (d, 1H, C_5-H, J=9.26 Hz), 7.3 (d, 1H, C_6-H, J=9.26 Hz), 7.52 (dd, 1H, C_{10}-H, J=8.00, 5.89 Hz), 8.56 (dd, 1H, C_{11}-H, J=8.00, 3.37 Hz), 8.72 (dd, 1H, C_9-H, J=5.89, 3.37 Hz), 9.68 (s, 1H, exch., NH) ; microanalysis for $C_{14}H_{13}N_4O_4$: found (calc) C-55.66 (55.99), H-3.95 (4.02), N-18.61 (18.66).

8.43. 7-Methoxy-5H-[1]benzopyrano[2,3-b]pyridine (129):

7-Methoxy-1-azaxanthone (73d) (2.0 g, 8.8 mmol) was added to 100 ml of methanol and sodium borohydride (0.66 g, 17.6 mmol) was added portionwise at room temperature. Completion of the reaction was indicated by the formation of a greenish yellow solution. Methanol was evaporated *in vacuo* and to the yellow residue was added 50 ml of water. The insoluble solid was filtered and dried. This intermediate alcohol was dissolved in 15 ml of glacial acetic acid and stirred at 0-5^{0}C. Sodium borohydride (0.6 g, 15.8 mmol) was added portionwise and the mixture, containing a white precipitate was poured into crushed ice (50 ml). The precipitate was filtered and recrystallized from acetone to give 7-methoxy-1-azaxanthone (129) (1.50 g, 80%). Mp 103^{0}C ; ir (KBr) (cm^{-1}): 2901 (C-H), 1581 (C=C) ; ^{1}H nmr spectra δ: 3.80 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.70 (d, 1H, C_6-H, J=3.60 Hz), 6.80 (dd, 1H, C_8-H, J=8.95, 3.23 Hz), 7.06 (dd, 1H, C_3-H, J=7.21, 5.47 Hz), 7.14 (d, 1H, C_9-H, J=8.95 Hz), 7.58 (dd, 1H, C_4-H, J=7.21, 2.98 Hz), 8.20 (d, br, C_2-H, J=5.47 Hz) ; microanalysis for $C_{13}H_{11}NO_2$: found (calc) C-72.66 (73.22), H-5.03 (5.20), N-6.59 (6.57).

8.44. 7-Hydroxy-5H-[1]benzopyrano[2,3-b]pyridine (130):

7-Methoxy-1-azaxanthene (129) (1.8 g, 8.4 mmol) was dissolved in 10 ml of 48% HBr and refluxed for 6 hrs. The resulting greenish yellow solution was poured into crushed ice (150 ml). A pale green precipitate which formed was filtered, dried and recrystallized from methanol to give 7-hydroxy-1-azaxanthene (130) (1.10 g, 65.7%). Mp 210^{0}C ; ir (KBr) (cm^{-1}): 3139 (br, OH), 1622 (C=N) ; ^{1}H nmr (DMSO-d_6) δ: 4.08 (s, 2H, CH_2), 6.70 (m, 2H, C_6-H, C_8-H), 7.00 (d, 1H, C_9-H, J=8.94 Hz), 7.24 (dd, 1H, C_3-H, J=7.10, 4.73 Hz), 7.85 (d, br, 1H, C_4-H, J=7.10 Hz), 8.20 (d, br, 1H, C_2-H, J=4.73 Hz) ; high resolution mass spectrum calculated for $C_{12}H_9NO_2$: 199.0633, found 199.0635

8.45. 8-Acetyl-7-hydroxy-5H-[1]benzopyrano[2,3-b]pyridine (131):

7-Hydroxy-1-azaxanthone (130) (1.10 g, 5.50 mmol) was placed in 80 ml of dry carbon disulfide and the mixture refluxed for 0.5 hr. Aluminum chloride (3.1 g, 23.2 mmol) and 1.6 ml (2.2 mmol) of acetyl chloride were then added and the reaction mixture refluxed overnight. Carbon disulfide was removed *in vacuo* and 25 ml of crushed ice was added to the residual oil. This was allowed to stand for 2-3 hr and the resulting white precipitate was filtered, dried and recrystallized from methanol to give 8-acetyl-7-hydroxy-1-azaxanthene (131) (1.0 g, 75.4%). Mp 110^{0}C ; ir (KBr) (cm^{-1}): 3468 (OH), 1753 ($COCH_3$) ; ^{1}H nmr ($CDCl_3$+DMSO-d_6) δ: 2.62 (s, 3H, $COCH_3$), 4.10 (s, 2H, CH_2), 6.8 (s, 1H, C_6-H), 7.06 (dd, 1H, C_3-H, J=7.0, 4.85 Hz), 7.54 (m, 2H, C_4-H, C_9-H), 8.2 (d, br, 1H, C_2-H, J=4.85 Hz), 11.90 (s, 1H, OH, exch.) ; microanalysis for $C_{14}H_{11}NO_3$: found (calc) C-69.18 (69.69), H-4.39 (4.59), N-6.17 (5.80) ; high resolution mass spectrum calculated 241.0738, found 241.0733.

8.46. 3-Acetyl-2-methylpyrido[3',2':5,6]pyrano[2,3-g](4H,11H)benzo-4-pyrone (132):

A mixture of 0.5 g (2.0 mmol) of 8-acetyl-7-hydroxy-1-azaxanthene (131), freshly fused sodium acetate (0.80 g, 9.70 mmol) and 5 ml of acetic anhydride was heated on an oil bath at 180^{0}C for 14 hr. The reaction mixture was then cooled, mixed with crushed ice and the resulting oil was takenup with dichloromethane (150 ml). This was washed with 5% sodium carbonate (3x50 ml) and finally with water. The dichloromethane was dried over sodium sulfate and evaporated *in vacuo*. Recrystallization of the residue from methanol afforded benzopyrone (132) (0.40 g, 62.8%). Mp 245^{0}C ; ir (KBr) (cm^{-1}): 1696 ($COCH_3$), 1630 (C=O) ; ^{1}H nmr ($CDCl_3$) δ: 2.54 (s, 3H, CH_3), 2.66 (s, 3H, $COCH_3$), 4.27 (s, 2H, CH_2), 7.10 (dd, 1H, C_9-H, J=7.42, 4.54 Hz), 7.30 (s, 1H, C_{12}-H), 7.60 (d, br, C_{10}-H, J=7.42 Hz), 7.94 (s, 1H, C_5-H), 8.27 (d, br, 1H, C_8-H, J=4.54 Hz) ; high resolution mass spectrum calculated for $C_{18}H_{13}O_4N$: found 307.0846, calculated 307.0844.

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